CLINICAL REVIEW

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Reviewer Name	Carolyn L. Yancey, MD
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Established Name	Celecoxib
(Proposed) Trade Name	CELEBREX
Therapeutic Class	NSAID), Selective COX-2 Inhibitor
Applicant	Pfizer, Inc. (Pfizer)
Priority Designation	P
Formulation	Oral capsule (sprinkle)
Dosing Regimen	Oral capsule: 50 mg (new); 100, 200 and 400 mg oral capsules
Indication	For the signs and symptoms of juvenile rheumatoid arthritis (JRA)
Intended Population	Patients with JRA
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1 EXECUTIVE SUMMARY

This Executive Summary is restricted to the evaluation of NDA 20-998, Supplement 021 with a proposed 50 mg capsule for the efficacy and safety of CELEBREX (celecoxib) for the proposed indication of the treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA), in patients who are ≥ 2 years to < 17 years of age, with body weight ≥ 10 kilograms (kg). CELEBREX was approved for adult patients with osteoarthritis (OA) and rheumatoid arthritis (RA) on December 31, 1998. The Division of Analgesia, Anti-Inflammatory and Ophthalmic Drug Products (DAAODP), HFD-550, issued a pediatric Written Request (WR) on April 21, 2000 and reissued a revised final pediatric WR on January 25, 2002 pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Pharmacia Corporation (acquired by Pfizer, Inc., April 2003) to obtain the needed pediatric information about CELEBREX (celecoxib) suspension. Pfizer, Inc. (Pfizer) responded to the pediatric WR on June 20, 2006 with the submission of NDA 20-998, Supplement 021, consisting of one phase 3 pivotal efficacy and safety study, three pharmacokinetic studies and one bioavailability study. The Food and Drug Administration (FDA) granted Pfizer six months of marketing exclusivity for CELEBREX (celecoxib) on August 23, 2006 based on the submitted pediatric Supplement 021, study of an investigational oral suspension of celecoxib in patients with JRA.

1.1 Recommendation on Regulatory Action

With NDA 20-998, Supplement 021, Pfizer is seeking approval for CELEBREX (celecoxib) capsule (50 mg) [pivotal Phase 3 Study 195 was conducted with an investigational oral suspension] administered as 50 mg BID (100 mg/day) or 100 mg BID (200 mg/day) for the treatment of the signs and symptoms of JRA in the pediatric population ≥ 2 years to < 17 years of age based on body weight. The proposed dosing scheme is: 50 mg BID for patients ≥ 10 kg to ≤ 25 kg and 100 mg BID for patients > 25 kg.

The recommended regulatory action for CELEBREX (celecoxib) for the proposed indication and dosing is approvable for the following rationale:

1) There was limited patient exposure to the proposed celecoxib dosages and the overall limited safety data of 24 weeks for longer-term use of celecoxib in JRA. The 12-week open-label extension was limited to high-dose celecoxib, 12 mg/kg/day, which is not included in the sponsor's proposed dose range. The low-dose celecoxib study was limited to the 12-week double-blind phase of Study 195;
2) The proposed dose scheme has the following issues:
    a) Exposes JRA patients to higher celecoxib doses, in mg/kg/day, than are in the approved adult RA label, taking into account pharmacokinetic data and safety data;
    b) Exposes, particularly, smaller weight children, to the highest doses (in mg/kg/day) which are associated with the increased risk for adverse events, and
    c) Higher celecoxib doses (in mg/kg/day) do not need to be administered to achieve efficacy as demonstrated with lower doses of celecoxib,

3) The longer-term safety risks from non-selective NSAIDs/COX-2 selective inhibitors in JRA patients is unknown, and
4) The increased risk of serious adverse cardiovascular events reported in adults, specifically, thromboembolic events as myocardial infarction and cerebrovascular accident as observed from 18-month studies with non-selective NSAIDs/COX-2 selective inhibitors.

The overall rationale for this recommended regulatory decision raise the overall issue of the need for longer safety observations with the proposed celecoxib doses in JRA patients and the need for a dose formulation which would support more accurate dosing and a lower dose for JRA patients, particularly, the smaller weight patients. A lower dose achieved sustained efficacy in the 12-week double-blind study. As the class of non-selective NSAID/COX-2 selective inhibitors continues to be studied, the Agency continues to monitor the safety profiles and longer-use risks of these drugs in adults and children.

The serious adverse cardiovascular events (thrombotic events) reported in adults prompted the September 2004 voluntary global market withdrawal of an approved non-selective NSAID/COX-2 selective inhibitor. It is recognized that thrombotic events, such as myocardial infarction and or cerebrovascular events, are extremely rare in children except in conditions of hyperlipidoses and hypercoagulable disease. The potential for lifetime exposure to non-selective NSAIDs/COX-2 selective inhibitors from childhood into adulthood for JRA patients with JRA raises safety concerns.

The sponsor studied a low-dose of celecoxib oral investigational suspension (6 mg/kg/day) and a high-dose celecoxib oral investigational suspension (12 mg/kg/day) in a 12-week randomized, double-blind, multicenter, active-controlled, parallel-group study with an optional 12-week open-label extension phase with high-dose celecoxib for a total study duration of 24-weeks. The active comparator studied was naproxen oral suspension administered as 15 mg/kg/day (7.5 mg/kg BID), 125 mg/5mL. Two different strengths of celecoxib oral suspension, 50 mg/5 ml and 100 mg/5 mL, were developed by the sponsor for Study 195.

The effect size of low-dose celecoxib suspension and high-dose celecoxib suspension demonstrated statistical non-inferiority to naproxen at the lower point estimate of -25% measured by the primary endpoint, the Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30% (JRA DOI 30) for JRA patients > 12 kg. There were an inadequate number of patients studied below 12 kg to reach a conclusion about efficacy. The composite endpoint of the response to the JRA DOI 30 criteria did not demonstrate statistical significance between the two celecoxib doses. The high-dose celecoxib treatment group trended with a higher numerical outcome by the JRA DOI 30.

The overall safety profile as reported for low-dose celecoxib and high-dose celecoxib demonstrated an adverse event profile that is consistent with the adult safety profile without the serious adverse cardiovascular findings reported in longer-term adult studies, specifically thromboembolic events, and without other findings (e.g., increased blood pressure and renal effect) known to be associated with use of this class of drug in adults. The overall adverse event profile was limited in the number of patients exposed to the proposed celecoxib doses of 100 mg/

day and 200 mg/day to make an adequate assessment of the safety in this JRA population. The exposure database submitted, **less than 100 patients** and **limited to 24 weeks** (12 weeks with low-dose and high-dose celecoxib and 12-weeks with high-dose celecoxib, open-label extension), is insufficient to adequately assess *efficacy and safety* of celecoxib suspension in the proposed dosages for JRA patients with body weight ≥ 10 kg to ≤ 12 kg and > 50 kg and insufficient to adequately assess *safety* at the proposed doses in JRA patients with body weight >12 kg. The data submitted is insufficient to adequately assess *efficacy and safety* at the proposed dosage of 100 mg in the smallest weight patients and 200 mg in the patients > 50 kg.

This reviewer concludes that there is adequate evidence of celecoxib efficacy based on the pivotal study and based on pooled sub-group analysis of JRA patients administered the proposed celecoxib doses of 100 mg/day or 200 mg/day. The pooled sub-group analysis (non pre-specified analysis) demonstrated that the higher-dose celecoxib was not required to achieve efficacy by the pre-specified criteria within the non-inferiority design. There was insufficient patient exposure to adequately assess *safety* at the proposed dosage and to adequately assess the longer-term safety risks from chronic use of this non-selective NSAID/COX-2 selective inhibitor, celecoxib, in JRA patients.

1.2 Recommendation on Postmarketing Actions

There are no postmarketing actions in this supplement.

1.2.1 Risk Management Activity

There is no pediatric risk management activity recommended at this time. See Section 9.5 Comments to Applicant.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments. See Section 9.5 Comments to Applicant.

1.2.3 Other Phase 4 Requests

As noted above in Section 1.2.2, there are no required Phase 4 commitments.

1.3 Summary of Clinical Findings

There were 242 JRA patients randomized in the pivotal Phase 3 Study 195. Of these patients, 138 JRA patients received celecoxib oral suspension, either as low-dose (6 mg/kg/day) [77 patients] or as high-dose (12 mg/kg/day) [82 patients]. The sponsor submitted one open-label food effect study, one open-label bioavailability study of celecoxib capsule and suspension, one relative bioavailability study of celecoxib capsule sprinkled onto applesauce, and one population pharmacokinetic study conducted as part of Study 195 including adult RA patients.

Within the non-inferiority study design of Study 195 for celecoxib oral suspension in JRA patients, the primary endpoint for evaluating efficacy was the proportion of patients achieving the JRA Definition of Improvement ≥ 30% (JRA DOI 30), a composite score of the 6 core variables. The low-dose and the high-dose celecoxib suspension achieved non-inferiority to the active comparator, naproxen, by the pre-specified non-inferiority margin of -25%. The proportion of patients achieving the JRA DOI 30 criterion over the 12-week double-blind phase was 69%, 80% and 67%, for the low-dose celecoxib 6 mg/kg/day, high-dose celecoxib 12 mg/kg/day, and naproxen 15 mg/kg/day, treatment groups, respectively.

The analysis of the 6 core set of variables of the JRA DOI 30 did not demonstrate a detectable difference among the two celecoxib treatment groups in comparison to the naproxen treatment group, except with the Physician's Global Assessment of Disease Activity (visual analogue scale, VAS) at Week-2, between low-dose celecoxib and naproxen ($p = 0.0138$), and with the number of joints with limited range of motion, comparing low-dose celecoxib to the high-dose celecoxib in which there was a detectable difference at Week-8 ($p = 0.0062$) and at Week-12 ($p = 0.0181$).

There were a total of 58 of 77 patients in the low-dose celecoxib group and 35 of 82 patients in the high-dose celecoxib group who received celecoxib in the doses consistent with the proposed label (100 mg to 200 mg/day). Through pooled sub-group analysis to assess efficacy, measured by the JRA DOI 30, in the weight categories (> 12 kg) of the proposed label, efficacy was maintained as:

- 70% (14/20 patients > 12 kg to ≤ 25 kg treated with low-dose celecoxib, 100 mg total daily dose);
- 91% (20/22 patients > 12 kg to ≤ 25 kg treated with high-dose celecoxib, 200 mg total daily dose);
- 81% (13/16 patients > 25 kg to ≤ 37 kg treated with low-dose celecoxib, 150 mg total daily dose); and
- 73% (11/15 patients > 37 kg to ≤ 50 kg treated with low-dose celecoxib, 200 mg total daily dose).

There was no representation of patients in the weight category of ≥ 10 kg and ≤ 12 kg in the low-dose celecoxib group, 2 patients in this same weight category in the high-dose celecoxib group, and 0 patients > 50 kg in either celecoxib group with a total daily dose of 100 to 200 mg/day.

The overall adverse event profile in the database for the low-dose celecoxib and high-dose celecoxib had no adverse events unexpected for non-selective NSAIDs/COX-2 selective inhibitors. There were no deaths reported in Study 195. The proportion of JRA patients who discontinued the double-blind phase of Study 195 due to adverse events was highest (7 events) in the high-dose celecoxib treatment group and equal (4 events each group) in the low-dose celecoxib and in the naproxen treatment groups. There were two unlabeled adverse event categories: 1) disseminated intravascular coagulation (DIC) in systemic onset JRA patients treated with high-dose celecoxib and low-dose celecoxib and 2) twitching reported with two different celecoxib suspension doses, 200 mg and 400 mg, in one adult patient in Study 1162.

Respiratory, thoracic and mediastinal disorders; eye disorders; and metabolic and nutrition disorders were the 3 body systems in which celecoxib demonstrated more adverse events than did naproxen, the active comparator. The most common adverse events in Study 195, across the 3 treatment groups, were in the gastrointestinal system, infections and infestations category and in the nervous system. The incidence of GI events was comparable in the naproxen group and in the low-dose celecoxib group.

The overall safety profile of adverse events for celecoxib demonstrates increased risk of adverse events with the higher-dose celecoxib compared to the lower-dose celecoxib. Early withdrawal during the double-blind phase secondary to an adverse event trends higher by the number of patients in the high-dose celecoxib (7 patients, 9%) than in the low-dose celecoxib group (4 patients, 5%). The serious adverse event profile of celecoxib suspension included experiences of severe epigastric pain/upper abdominal pain, nausea and vomiting; severe allergic reaction with severe flare of asthma; myopericarditis with chest pain; severe flare of systemic JRA with a positive DIC panel of laboratory tests; moderate and severe elevation of hepatic enzymes; moderate and mild elevation of creatinine phosphokinase; and hematuria. Naproxen, the active comparator, was associated with gastrointestinal experiences of abdominal pain, nausea and vomiting; gastritis; headaches, and severe exacerbation of systemic JRA.

In Study 195, there was only one report of hypertension as an adverse event and this occurred in the naproxen treatment group. As hypertension is a well known reported adverse event with non-selective NSAIDs/COX-2 selective inhibitors in adults, the concern for possible under-reporting of hypertension in Study 195 may have occurred due to the method of collection of blood pressure data and the high threshold for defining hypertension as an adverse event in these pediatric patients.

The sponsor reported 9 patients with serious adverse events (SAEs). These experiences included gastrointestinal events (nausea, vomiting, epigastric pain, hepatitis), exacerbation of asthma, flare of JRA, disseminated intravascular coagulation, chest pain, and myopericarditis.

Reported laboratory adverse events for elevated hepatic enzymes were only reported in the low-dose and the high-dose celecoxib treatment groups; hematuria and proteinuria causing withdrawal from Study 195 were reported in one patient in the naproxen group and hematuria alone was reported in one patient in the low-dose celecoxib group causing withdrawal from the study. In this limited safety data, celecoxib appears to involve more risk for elevation of hepatic enzymes than naproxen, the active comparator.

Patients with systemic onset JRA experienced serious adverse events in both the celecoxib treatment groups and in the naproxen group. There were 22 patients (9%) whose JRA disease onset included systemic features: 4 (5.2 %), 10 (12 %) and 8 (10 %) in the low-dose celecoxib, high-dose celecoxib and the naproxen treatment groups, The SAEs experienced by patients with systemic JRA demonstrated 1 of 4 (25%) in the low-dose celecoxib group (altered mental status, nausea, vomiting, elevated hepatic functions, abnormal coagulation laboratory tests, Cytomegalovirus (CMV) hepatitis), 2 of 10 (20%) in the high-dose celecoxib group (chest pain, myopericarditis, severe flare of JRA, abnormal coagulation laboratory tests; severe gastritis) and

2 of 8 (25%) in the naproxen treatment group (severe flare of JRA, abdominal pain, nausea, vomiting; hematuria and proteinuria).

The patient exposure and the safety data submitted were insufficient to adequately assess *safety* at the proposed celecoxib doses (100 mg/day or 200 mg/day) for body weight ≥ 12 kg. As the dose scheme in Study 195 was administered as a fixed-volume dose, there is variability within each treatment arm for the amount of study medication actually received by the patent. See Section 7.1 Methods and Findings (under the Integrated Review of Safety) for details of the dose scheme in Study 195.

In the 12-week double-blind phase, 39 of 77 patients (51%) in the low-dose celecoxib (6 mg/kg/ day) treatment group actually received < 5 mg/kg/day of celecoxib and 47 of 82 patients (57%) in the high-dose celecoxib (12 mg/kg/day) treatment group actually received < 10 mg/kg/day of celecoxib. In the 12-week open-label phase, 63 of 202 patients (31%) in the high-dose celecoxib (12 mg/kg/day) treatment group actually received < 10 mg/kg/day. The fixed volume dosing scheme is associated with a range of doses around the target study dose.

Sub-group analysis for the effect of celecoxib and concomitant administration of methotrexate did not demonstrate any significant interaction. Sustained efficacy was demonstrated in patients who received celecoxib within the total daily dose range proposed by the sponsor and concomitant methotrexate.

Sub-group analysis of JRA by onset-type, polyarticular or pauciarticular course, demonstrated a detectable difference with the JRA DOI 30 response rate ($p = 0.0110$) for polyarticular course JRA treated with high-dose celecoxib at Week 12 compared to the naproxen. The study arms were balanced for age, JRA course type and gender, in view of the overall higher incidence of JRA in girls than in boys.

1.3.1 Brief Overview of Clinical Program

Celebrex (celecoxib) oral suspension (50 mg/5 mL and 100 mg/ 5 mL) is a selective cyclogenase-2 (COX-2) inhibitor which inhibits prostaglandin synthesis. Celecoxib is indicated in adults for the relief of the signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA), acute pain and primary dysmenorrhea, ankylosing spondylitis (AS). In NDA 20-998 pediatric Supplement 021, celecoxib was studied for the indication of relief of signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients ≥ 2 years to ≤ 16 years old.

- CELEBREX is an approved non-steroidal anti-inflammatory drug (NSAID)/COX-2 selective inhibitor, with an oral route of administration;
- The proposed indication for this pediatric efficacy and safety supplement is for the treatment of signs and symptoms of juvenile rheumatoid arthritis (JRA).
  Note: The sponsor did not specify the type onset course of JRA;
- There is one pivotal efficacy and safety trial (Study N49-01-01-195), hereinafter **Study 195**, three pharmacokinetic studies (Study N49-98-02088), hereinafter **Study 088,** study A3191162, hereinafter **Study 1162**, Study A3191202, hereinafter **Study 1202**, and one

population pharmacokinetic study including adult RA patients, research report (RR754-00049), hereinafter **RR- 049**, performed as a subset of the Phase 3 Study 195.

- Celecoxib is not approved for use in pediatric patients. There is off-label pediatric use information available through spontaneous reporting. There were 30 cases reported through the Adverse Event Reporting System (AERS) database for all serious and non-serious pediatric adverse events cited between 12/31/98 and 08/10/06 for celecoxib. There were 88 cases retrieved, of which 31 spontaneous postmarketing reports were noted.
- The total number of patients enrolled in the studies are as follows:
[See Table 1, Section 4.2]

Study 195 (Pivotal), Clinical Efficacy and Safety in JRA (12-Week Double-Blind Phase)

Randomized: 242 Patients with JRA
Treated: 242 (77 patients were treated in the low-dose celecoxib 6 mg/kg/day (3 mg/kg BID) as 50 mg/5 mL treatment group; 82 patient were treated in the high-dose celecoxib 12 mg/kg/day (6 mg/kg BID) as 100 mg/5 mL treatment group; and 83 patients were treated in the naproxen 15 mg/kg/day (7.5 mg/kg BID) as 125 mg/5 mL treatment group)
Completed: 212 (10 patients who completed the double-blind phase of Study 195 did not enter the open-label extension phase)

Study 195, Open-Label Extension Phase (12-Weeks)

Randomized: 202 Patients with JRA
Treated: 202 (All patients entered in the open-label received high-dose celecoxib 12 mg/kg/day (6 mg/kg BID) as 100 mg/5 mL.
Completed: 195

Study RR-049, Population Pharmacokinetic Study

Randomized: 43 Adults with RA
73 JRA patients (low-dose celecoxib)
79 JRA patients (high-dose celecoxib)
Completed: 36 Adults with RA
73 JRA patients (low-dose celecoxib)
79 JRA patients (high-dose celecoxib)

Study 088, Open-Label, Food Effect Study

Randomized: 24 Adults, Healthy
Treated: 24
Completed: 24

Study 1162, Open-label Bioavailability Study of Celecoxib Capsule and Suspension

Randomized: 21 Adults, Healthy
Treated: 21
Completed: 17

Study 1202, Relative Bioavailability of Celecoxib Capsule Content Sprinkled on Applesauce

Randomized: 24 Adults, Healthy
Treated: 24
Completed: 24

- Overall the number of patients in the safety data base and the extent of subject years of exposure were 242 juvenile patients, 17 to 18 years of subject-years in the double-blind phase and 14 to 16 subject years in the open-label phase, respectively. There were 43 adult RA patients who participated in the population PK study and 69 healthy adult subjects who participated in Study 088, 1162 and 1202.
- The pertinent clinical data sources used for this review include the sponsor's electronic files and hard copy volumes submitted to the FDA, Center for Drug Evaluation and Research (CDER), HFD-170, the Division of Analgesia, Anesthesia and Rheumatology Products (DAARP).

1.3.2 Efficacy

The pivotal Study 195 was a 12-week, randomized, double-blind, active-controlled, parallel-group, multicenter, non-inferiority study comparing the efficacy and safety of low-dose celecoxib oral suspension, 6 mg/kg/day (3 mg/kg BID), and high-dose celecoxib oral suspension 12 mg/kg/day (6 mg/kg BID) compared to naproxen suspension, 15 mg/kg/day (7.5 mg BID) as 125 mg/5 mL, in JRA patients with an optional 12-week open-label extension treatment phase with only high-dose celecoxib suspension. The sponsor developed two different oral investigational suspensions, 50 mg/ 5mL and 100 mg/5 mL, for Study 195. The total duration of Study 195 was 24 weeks.

The primary efficacy endpoint was the Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30 % (JRA DOI 30), a responder rate, and the secondary endpoints were the individual 6 core set variables of the JRA DOI 30. Other evaluations were the Parent's Assessment of Child's Arthritis Pain (visual analogue scale [VAS]), CHAQ subsection, and the Pediatric Quality of Life Inventory, as well as, various definitions of improvement for use in the JRA population (JRA DOI-50, JRA DOI-70, and JRA DOI-30 in pauciarticular and polyarticular JRA, separately).

The pre-specified criterion for the non-inferiority trial design was claimed if the lower limit of the 95% 2-sided confidence interval for the difference in the percent responders (celecoxib – naproxen) was above -25%. The difference for celecoxib, 6 mg/kg/day – naproxen, 15 mg/kg/day was +1.36% (-13.08%, 15.80%) with a p-value of 0.8535 and for celecoxib, 12 mg/kg/day – naproxen, 15 mg/kg/day was +13.02% (-0.22%, 26.25%) with a p-value of 0.0568.

The proportion of patients achieving the **JRA DOI 30** criterion over the 12 week double-blind study was **69%, 80% and 67%,** for the **low-dose celecoxib suspension**, 6 mg/kg/day, **high-dose celecoxib suspension**, 12 mg/kg/day and active comparator, **naproxen**, 15 mg/kg/day treatment groups, respectively. The composite endpoint of response to the JRA DOI 30 criteria

did not demonstrate statistical significance between the high-dose celecoxib treatment group and low-dose celecoxib treatment group, though the high-dose celecoxib treatment group demonstrated a greater numerical outcome by the JRA DOI 30 (percent responder).

The proportion of JRA patients who discontinued the double-blind phase of Study 195 due to adverse events was highest (7 events) in the high-dose celecoxib treatment group, and equal (4 events each group) in the low-dose celecoxib and in the naproxen treatment groups. Discontinuations due to lack of efficacy were 2, 1 and 4 patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups.

Analysis of the secondary endpoints demonstrates that both the low-dose and high-dose celecoxib are non-inferior to naproxen in each of the core set variables. When comparing the low-dose celecoxib (6 mg/kg/day) treatment group to the high-dose celecoxib (12 mg/kg/day) treatment group for the number of joints with limited range of motion, there were two time points with a detectable difference, at Week-8 with a difference of 1.45 [0.42, 2.49], p=0.0062, and at Week-12 was a detectable difference of 1.44 [0.25, 2.63], p=0.0181.

In the other analyses in the open-label phase, using the Pediatric Quality of Life Inventory, Physical Health Summary of the Child's Self-Report, the low-dose celecoxib appeared to demonstrate better treatment effect, as measured by the mean change from Baseline to Week 24, 12.13 (SD 20.74).

The response rates for the **JRA DOI 50** were **56%, 61% and 55%**, and for the **JRA DOI 70** were **25%, 37% and 33%,** for the low-dose celecoxib, high-dose celecoxib and the naproxen group, respectively, in the double-blind 12-week phase. There was a detectable difference with the JRA DOI 30 response rate (p=0.0110) for polyarticular course JRA treated with high-dose celecoxib at Week 12 compared to the naproxen treatment group. The low-dose celecoxib treatment group demonstrated non-inferiority compared to naproxen treated patients.

The overall limitations in Study 195 are the inadequate amount of patient data to adequately assess *efficacy and safety* of celecoxib oral suspension at the proposed dosage of 100 mg total daily dose (50 mg BID) and 200 mg total daily dose in the weight categories of ≥ 10 kg to ≤ 12 kg and > 50 kg. [Note: There were 0 patients studied in the weight category of ≥ 10 kg and ≤ 12 kg in the low-dose celecoxib treatment group, 2 patients studied in this same weight category in the high-dose celecoxib treatment group, and 0 patients > 50 kg in either low-dose or high-dose celecoxib treatment groups, with total daily dose of 100 mg to 200 mg/day.]

1.3.3 Safety

The overall adverse event profile for the low-dose celecoxib (12-week data) and high-dose celecoxib (24-week data) in the limited database had no adverse events unexpected for non-selective NSAIDs and or COX-2 selective inhibitors. There is a trend for increased *serious adverse events* with high-dose celecoxib more than with low-dose celecoxib in Study 195. Five of 9 patients reported by the sponsor with SAEs were treated with high-dose celecoxib and 4 of these 9 patients were treated with low-dose celecoxib. None of the SAEs reported by the sponsor

included the active comparator, naproxen. There were 3 patients who experienced severe adverse events. There were increased *severe adverse events* with high-dose celecoxib, 2 patients were treated with high-dose celecoxib and 1 patient was treated with naproxen.

The data submitted at the proposed doses is insufficient to adequately assess the longer-term adverse events such as hypertension and other cardiovascular risks in JRA, though thromboembolic events, such as myocardial infarction and cerebrovascular accident are rare in JRA. Specific to Study 195, the data is insufficient to adequately assess safety in patients with body weight > 25 kg to ≤ 37 kg and > 37 kg to ≤ 50 kg, as there were a total of 16 and 15 patients studied in these two weight ranges, respectively. Using sub-group analysis of pooled data from 20 patients (> 12 kg to ≤ 25 kg) treated with low-dose celecoxib, (6 mg/kg/day) and 28 patients (> 12 kg to ≤ 25 kg) treated with high-dose celecoxib (12 mg/kg/day) efficacy is maintained in these 48 patients using the JRA DOI 30. Exposure data to celecoxib, however, is inadequate to assess safety in these same weight categories.

In view of the existing armamentarium treatment approved for the indication of relief of the signs and symptoms of JRA, celecoxib oral suspension at the low-dose (6 mg/kg/day) demonstrates efficacy comparable to naproxen oral suspension, 15 mg/kg/day. Safety data is available for celecoxib administered as > 200 mg to ≤ 600 mg total daily dose, which are higher than the sponsor's proposed celecoxib dosage and administration.

The safety profile of celecoxib as 100 mg/day and 200 mg/day needs to be adequately studied to assess the longer-term safety risks in JRA patients. The high-dose celecoxib (12 mg/kg/day) treatment group trends with increased adverse events. The trend of increased AEs was demonstrated with respect to the **respiratory, thoracic and mediastinal infection events, elevation of hepatic enzymes**, and **patients with systemic onset JRA experiencing a flare of their disease including abnormal coagulation laboratory tests consistent with disseminated intravascular coagulation (DIC)**. Hypertension, as an adverse event, was not reported in either celecoxib treatment group and raises concern for possible under-reporting of this adverse event in patients treated with non-selective NSAIDs/COX-2 selective inhibitors. As acknowledged by the sponsor, the method of monitoring and reporting hypertension in Study 195 was aligned with adult monitoring of systolic and diastolic blood pressure rather than with pediatric monitoring of systolic and diastolic blood pressure.

Due to the limited safety data in Study 195 (12-week double-blind phase with the low-dose and high-dose of celecoxib and 12-week open-label extension phase with only the high-dose of celecoxib), the proposed dose scheme which proposes higher doses (in mg/kg/day), particularly in the smaller weight children, than are needed to achieve efficacy, the unknown longer-term safety risks of this non-selective NSAID/COX-2 selective inhibitor in JRA patients and the increased concern about the reported serious adverse cardiovascular events (thromboembolic) of non-selective NSAID/COX-2 selective inhibitors with treatment of 18 months duration in adults with various conditions, this reviewer recommends approvable as the recommended regulatory action. In Section 9.5 of this review are recommendations to the sponsor for additional study of celebrex which could later support approval of this selective NSAID/COX-2 selective inhibitor in JRA patients.

1.3.4 Dosing Regimen and Administration

The celecoxib oral suspension doses in the double-blind phase of Study 195 were low-dose celecoxib (6 mg/kg/day) as a 50 mg/5 mL suspension and high-dose celecoxib (12 mg/kg/day) as a 100 mg/5mL suspension. In the open-label extension phase of Study 195, all patients were entered into a high-dose celecoxib (12 mg/kg/day) treatment group, regardless of their treatment group assignment in the double-blind phase. The sponsor's proposed dosing for patients with JRA is based on total body weight: celecoxib capsule (50 mg) 50 mg BID (100 mg/day) for patients ≥ 10 kg to ≤ 25 kg, and 100 mg BID (200 mg/day) for patients > 25 kg.

This medical reviewer completed non pre-specified sub-group analysis of efficacy in the JRA patients who received a total daily dose as proposed in the label (100 mg/day or 200 mg/day). These data are as follows in the weight categories as defined by the sponsor: there were 20 patients (> 12 kg to ≤ 25 kg) received low-dose celecoxib, 16 patients (> 25 kg to ≤ 37 kg) received low-dose celecoxib, 15 patients (> 37 kg to ≤ 50 kg) received low-dose celecoxib; and 22 patients (> 12 kg to ≤ 25 kg) received high-dose celecoxib. There were 0 patients studied with total body weight ≥ 9 kg to ≤ 12 kg, who received low-dose celecoxib, and 0 patients studied with total body weight > 50 kg, who received low-dose celecoxib as proposed. See Table 34.

There are concerns that the proposed dose scheme recommends higher doses of celecoxib for the smaller weight patients and poses undue risk of increased adverse events. See Section 1.3.3 Safety Summary for observations from the assessment of the fixed-volume dose scheme in Study 195 and Section 7.1 Safety. Also see the Clinical Pharmacology review by Srikanth Nallani, PhD and Atul Bhattaram, PhD.

The sponsor explained significant technical challenges in commercializing the investigational suspension formulation and other pediatric formulations, such as an orally disintegrating or a chewable tablet. The sponsor estimated that a minimum of 2 to 3 years will be needed to identify necessary changes in the formula and in the manufacturing process, confirm the bioavailability/bioequivalent of the final suspension relative to the investigational suspension used in Study 195, and to gather International Conference for Harmonization (ICH) stability data to support an NDA for the suspension formulation. Pfizer proposed discontinuing the development of the oral suspension formulation and using the capsule formulation in order to provide a timely therapeutic alternative for patients with JRA. Oral suspension formulation supports more accurate dosing for pediatric patients.

See the CMC review by Stuart Zimmerman, PhD for additional information about the development program for a celecoxib suspension and for the review of the proposed 50 mg capsule.

1.3.5 Drug-Drug Interactions

Celecoxib is approved for various indications in adult patients. Drug-drug interaction studies were completed with the original NDA 20-998 submission. Though the pre-specified protocol was not designed for efficacy sub-analyses, this medical reviewer completed an analysis of

efficacy for celecoxib and the co-administration of methotrexate and or biologic response modifiers in this supplement. See Section 6.0 Efficacy.

1.3.6 Special Populations

The non-selective NSAID/COX-2 selective inhibitor, celecoxib, has been studied in adult special populations of geriatrics, adults with hepatic insufficiency and adults with renal insufficiency. Celecoxib has also been studied for pharmacokinetic differences by race under the original NDA 20-998. Clinical studies demonstrate gastrointestinal and cardiovascular safety issues with long-term administration of celecoxib in adult patients with various conditions. Currently, Pfizer is conducting a 20,000-person international trial to further assess the safety risks of long-term administration with celecoxib. Within the class of non-selective NSAIDs/COX-2 selective inhibitors, one approved product, VIOXX (rofecoxib), was voluntarily withdrawn by Merck from the global market on September 30, 2004 because of the serious adverse cardiovascular safety risks.

Juvenile Rheumatoid Arthritis
There are 3 subtypes of JRA characterized by the clinical course of onset: pauciarticular (oligoarticular), polyarticular and systemic onset JRA with the frequency of cases as 60%, 30% and 10%, respectively. JRA is one of the most common rheumatic diseases of childhood and the leading cause of childhood disability, affecting approximately 30,000 to 60,000 in the United States and Canada. The pivotal Study 195 included enrollment of 128 pauciarticular, 114 polyarticular JRA patients and 22 patients with onset of systemic JRA (without active systemic features). This study includes an exploratory analysis of pauciarticular versus polyarticular onset course differences in the efficacy response to celecoxib.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- CELEBREX is an approved non-selective NSAID/COX-2 selective inhibitor, with an oral route of administration;
- The proposed indication is for the treatment of signs and symptoms of juvenile rheumatoid arthritis (JRA);
- Celecoxib is pharmacologically distinct from non-steroidal anti-inflammatory drugs.

2.2 Currently Available Treatment for Indications

Juvenile rheumatoid arthritis continues to have limited approved NSAIDs and, currently, two approved non-selective NSAID/COX-2 selective inhibitors, VIOXX (rofecoxib) and MOBIC (meloxicam). VIOXX (rofecoxib) was approved August 18, 2004 for the indication of the relief of signs and symptoms of pauciarticular and polyarticular JRA in patients ≥ 2 years and ≤ 17 years of age, based on a 12-week double-blind, double-dummy, active-controlled trial and a 52-week, open-label, active-controlled extension trial. On September 30, 2004, the sponsor

voluntarily withdrew the rofecoxib moiety from the global market because of serious adverse cardiovascular safety concerns.

MOBIC (meloxicam), considered a non-selective NSAID/semi-selective COX-2 inhibitor in the United States, was approved August 18, 2005 for the indication of the relief of signs and symptoms of JRA in the pediatric population aged 2 years through 17 years. The meloxicam approval was based on 3 clinical trials: a 12-week randomized, double-blind, double-dummy, parallel group and a 12-week double-blind extension; a 12-week randomized, double-blind, double-dummy, parallel group, active-controlled phase and a 40-week open-label extension; and a 52-week open-label study of meloxicam.

Aspirin (salicylates) are the oldest approved NSAID with an indication for treating the signs and symptoms of JRA. Currently, the most commonly dispensed NSAIDs by retail pharmacies in pediatric patients 0-16 years of age are ibuprofen, naproxen, tolmetin sodium, meloxicam, indomethacin, and oxaprozin.* Pediatric use for most of these products is significantly lower than the proportion of prescriptions dispensed for adults, defined as 17 years and older.
** Note: Information extracted from a Consult from the Division of Surveillance, Research and Communication Support, HFD-410, Office of Surveillance and Epidemiology.*

2.3 Availability of Proposed Active Ingredient in the United States

Celecoxib is a non-selective NSAID/COX-2 selective inhibitor and, as explained by the sponsor, is pharmacologically distinct from non-selective NSAIDs such as diclofencac, ibuprofen and naproxen that inhibit COX-1 and COX-2 isoforms of the enzyme. Celecoxib was first approved in 1998 for OA and RA and has achieved additional clinical indications as cited in Section 1.3.1 Brief Overview Clinical Program.

The Food and Drug Administration (FDA), as of April 2005, required that all NSAID labels be revised to reflect the cardiovascular and gastrointestinal safety risks of non-selective NSAIDs and COX-2 selective inhibitors. This decision was prompted by reports demonstrating increased cardiovascular risks in persons who were studied for the prevention of colon polyps. Merck voluntary withdrew VIOXX (rofecoxib) September 2004 in response to the prevention of colon polyps study which reported increased thrombotic cardiovascular risks with non-selective NSAIDs/COX-2 selective inhibitors. The CELEBREX label was revised to include a boxed warning including the cardiovascular risk, the contraindication for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery and the gastrointestinal risk of NSAIDs, including CELEBREX, causing an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach and intestines, which can be fatal. The cardiovascular safety concerns, specifically, thromboembolic events, with non-selective NSAID/COX-2 selective inhibitors remains unresolved. A large 20,000 person medical outcomes study is being conducted by Pfizer to investigate the cardiovascular and gastrointestinal risks for patients administered celecoxib.

2.4 Important Issues with Pharmacologically Related Products

See Section 2.3 above.

2.5 Pre-submission Regulatory Activity

The regulatory history for CELEBREX (celecoxib) and Supplement 021 is as follows:

- CELEBREX was initially approved on December 31, 1998 for the indications of osteoarthritis (OA) and rheumatoid arthritis (RA), approved to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care (NDA 21-156) in December 1999, approved for the indication of the management of acute pain in adults and the treatment of primary dysmenorrhea October 2001 and most recently approved in Ankylosing Spondylitis August 2005.
- August 31, 1999 in reference to Section 505A of the Federal Food, Drug and Cosmetic Act, qualifying for Pediatric Exclusivity and the Agency's update (May 20, 1999) List of Approved Drugs for Which Additional Pediatric Information Produce Health Benefits in the Pediatric Population [Section 5059c]), Searle submitted a Proposed Pediatric Study Request (PPSR) for celecoxib in IND 48,395. The study was originally submitted as a randomized, blinded, withdrawal efficacy and safety trial of 3 months duration. The objectives were to evaluate the efficacy of two doses of celecoxib compared to a standard active control (equivalence or superiority hypothesis) to evaluate the efficacy of celecoxib by dose-response (a difference hypothesis), and to evaluate the safety relative to the active control (descriptive statistics).
- February 24, 2000 teleconference meeting minutes documented Searle's original proposal for a withdrawal type study. FDA recommended a more traditional design and proposed a 1 to 2-arm study drug versus active control, 3-month duration with the primary endpoint as the JRA Definition of Improvement ≥ 30%. FDA explained that an active comparator would be allowed versus a placebo control, as the change in study design had been discussed and supported by the pediatric rheumatology community. The recommendation for an Arthritis Advisory Committee meeting was also discussed in view of the new area of drug class and the use of the instrument, the JRA DOI ≥30%. FDA confirmed that the Written Request would comply with both the Pediatric Rule and the Exclusivity requirements, whether or not the outcome of the study was successful.
- April 21, 2000 a Written Request was issued by FDA to Searle. Statistical Information: "Three efficacy hypotheses should be formally tested-two equivalence (non-inferiority) tests, ruling out a clinically meaningful difference between each of the two celecoxib doses and the active control; and one difference test comparing the two celecoxib dosages used. Another option is to demonstrate superiority of celecoxib to the active comparator.
- The Best Pharmaceuticals for Children's Act was passed by Congress on January 4, 2002.
- January 25, 2002 a revised WR was issued to Searle by FDA. Study reports should be submitted to the Agency on or before December 31, 2005.
- February 4, 2002 further revisions in the WR were issued to Searle by FDA. Study reports should be submitted to the Agency on or before June 30, 2006.
- June 11, 2002 Pharmacia submitted the Chemistry, Manufacturing and Controls (CMC) information for celecoxib oral suspension, naproxen oral suspension and placebo for both these products.
- September 6, 2002 the protocol N49-01-02-195, "Clinical Protocol for 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" was originally filed.

- Pharmacia was acquired by Pfizer, Inc on April 16, 2003.
- November 19, 2003 Protocol 195 was further amended in the eligibility criteria and safety assessments.
- December 18, 2003 Protocol A3191162, an Open-Label, Randomized, 4-Period, 4-Treatment, Relative Bioavailability Study of Celecoxib Commercial Capsule and Suspension Formulations in Healthy Volunteers" was filed by Pfizer Pharmaceutical Group. Pfizer noted it remains necessary to assess the bioavailability between the oral suspension and the commercial capsule, in order to correlate the JRA study results to the drug used commercially.
- September 30, 2004 VIOXX was voluntarily withdrawn by Merck from the global market due to the reporting of serious cardiovascular adverse event from placebo-controlled study with rofecoxib. At the time, Pfizer also submitted data that reported valdecoxib (BEXTRA) is associated with increased cardiovascular risk when used to treat pain in the setting of post-coronary artery by-pass surgery. The combination of these reports suggests that cardiovascular adverse events may be a phenomenon that is common to all non-selective/COX-2 selective inhibitors.
- December 23, 2004 Office of Counterterrorism and Pediatrics (OCTAP) stated that they had safety concerns about the current study of celecoxib oral suspension in pediatric patients and the Division of Analgesia, Anti-inflammatory and Ophthalmic Drug Products and OCTAP held a teleconference with Pfizer to discuss the safety concerns of celecoxib.
- October 10, 2005 Type B meeting request, Pre-sNDA for JRA to discuss the dosage form, dose(s) and method of administration in JRA patients and the adequacy of the conducted studies to support the JRA indication.
- January 10, 2006 Pfizer, Inc requested to meet with the FDA to seek input on the adequacy of the efficacy, safety and pharmacokinetic (PK) data obtained in Study 195.
- April 2006 CMC Study submitted to the Agency.
- June 20, 2006, sNDA 20-998, Supplement 021 submitted to the Agency as an expedited review (6 months).
- August 23, 2006 Pediatric Exclusivity granted to Pfizer based on Supplement 021.

2.6 Other Relevant Background Information

This section does not apply to Supplement-021 review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

See the Clinical Pharmacology review by Srikanth Nallani, PhD and Atul Bhattaram, PhD.

See the Pharmacology/Toxicology review by Gary Bond, PhD.

See the Chemistry, Manufacturing and Controls review by Stuart Zimmerman, PhD, and Ramesh Raghavachari, PhD.

See the Statistic review by Katherine Meaker, PhD.

3.1 CMC (and Product Microbiology, if Applicable)

An industry pre-NDA meeting with the Division of Anesthesia, Analgesia and Rheumatology Products on January 10, 2006 includes Chemistry, Manufacturing and Controls (CMC) issues concerning the 50 mg capsule, and confirmation of the (b) (4) shelf life. The CMC Division made recommendations for commercializing the 50 mg capsule and testing the 50 mg capsule as a sprinkle on applesauce. Information to clarify the technical challenges in commercializing the investigational suspension formulation is still being evaluated at this writing. Further clarification about why a suspension was not developed is under review. See the CMC review by Stuart Zimmerman, PhD and Ramesh Raghavachari, PhD.

3.2 Animal Pharmacology/Toxicology

The toxicity of celecoxib was characterized by two juvenile animal models to support the safety of treating JRA patients. Celecoxib appeared to produce no adverse effects on juvenile animal growth or development. There are pharmacology toxicology findings from administration of celecoxib in **gastrointestinal trac**t, **skin** and in the **male reproductive tract** effects. It appears that juvenile rats are more sensitive to celecoxib-caused gastrointestinal toxicity (ulceration with peritonitis) and that juvenile dogs are more sensitive to celecoxib treatment-induced dermal lesions (ulcerations). The male reproductive tract effects (unilateral or bilateral enlargement of testes and prominent tubules in the epididymal fat pad) and microscopic changes (minimal to slight unilateral or bilateral dilatation of seminiferous tubular dilatation and epididymal hypospermia) appear to be rat-specific. The effect of these reported findings remains undefined as to the effect in humans. See the Pharmacology/Toxicology review by Gary Bond, PhD.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data was submitted by the sponsor in an electronic format to the Division of Analgesia, Arthritis, and Rheumatology Products (DAARP), the Center for Drug Evaluation and Research (CDER), the Electronic Document Room (EDR). The data quality of the submission was acceptable to this medical reviewer. Additional sources of clinical data used for this review include: NDA 21-156 CELEBREX (celecoxib) and NDA 20-998 CELEBREX (celecoxib), IND 48,395 (CELEBREX (celecoxib) including Division files and related reviews from the following individuals: Statistical review by Katherine Meaker, PhD; Clinical Pharmacology review by Srikanth Nallani, PhD; Chemical Manufacturing and Controls (CMC) Ramesh Raghavachari, PhD and Stuart Zimmerman, PhD; and Pharmacology/Toxicology review by Gary Bond, PhD. Consultations within the FDA were obtained from the Division of Scientific Investigations (DSI), and the Office of Drug Safety (ODS). No external consultations were obtained by the FDA for this review.

An Arthritis Advisory Committee (AAC) meeting is scheduled for November 29, 2006. See Section 8.5 Advisory Committee Meeting of this review.

4.2 Tables of Clinical Studies

Pfizer submitted four clinical trial study reports and one research report from Study 195 in the pediatric supplement 021: there were two pharmacokinetic (PK) studies (Study 088 and 1162) in adults; one Chemistry Manufacturing Controls (CMC) study (Study 1202) in adults with celecoxib capsule contents sprinkled on applesauce; one Phase 3 pivotal clinical study (Study 195) for safety and efficacy in patients with juvenile rheumatoid arthritis with an optional 12-week, open-label extension study to the Phase 3 pivotal study; and one research report (RR 049) from the Phase 3 pivotal study for population pharmacokinetics in adult patients with rheumatoid arthritis (RA) and in children and adolescents with JRA. See Table 1.

Table 1. Summary of Studies for Celecoxib Pediatric Filing, NDA 20-998, Supplement 021

Protocol #, Study, Total # Patients Randomized	**Entry Criteria; Age; Diagnosis**	**Objective**	**Study Design**	**Treatment**
N49-01-02-195 (Study 195) <u>12-Week Double-blind Study</u>: Total # patients randomized: 242 <u>Optional 12-Week Open-label Extension:</u> Total # patients randomized: 210.	≥ 2 to ≤ 16 years of age with polyarticular, pauciarticular or systemic JRA (inactive systemic features).	To study the proportion of patients that improve, by the JRA DOI 30 criteria, with two different doses of celecoxib and naproxen	12-week, randomized, double-blind, multicenter, active-controlled, parallel group study to evaluate the safety and efficacy of celecoxib suspension compared to naproxen suspension in patients with JRA, with an optional 12-week, open-label treatment phase to evaluate tolerability and durability.	Treatment Groups: Celecoxib oral suspension, 6 mg/kg /day (3 mg/kg BID as 50 mg/5mL) cohort; celecoxib oral suspension, 12 mg/kg/day (6 mg/kg BID as 100 mg/5mL) cohort; and naproxen oral suspension, 15 mg/kg/day (7.5 mg/kg BID as 125mg/5mL) cohort. <u>Optional Open-label Extension Treatment Groups</u>: All patients continuing in the open-label phase of the study started open-label celecoxib 12 mg/kg/day (6 mg/kg BID as 100mg/5mL) oral suspension on the day following the Week 12 visit. Naproxen oral suspension 15mg/kg/day (7.5

Protocol #, Study, Total # Patients Randomized	Entry Criteria; Age; Diagnosis	Objective	Study Design	Treatment
				mg BID as 125mg/5mL) oral suspension was the active comparator.
N49-98-02-088 (Study 088) Total # patients randomized: 24 (healthy adults)	Healthy adults.	To assess the dose proportionality and the effect of a high fat meal on the PK profile of celecoxib in healthy adults.	Open-label, randomized, single dose, 4-way crossover study	Treatment Groups: Celecoxib 50 mg capsules; 50 mg capsule, fasting; 50 mg with high-fat breakfast; 100 mg capsule fasting, 100 mg capsule with high-fat breakfast.
A3191162 (Study 1162) Total # patients randomized: 21	Healthy adults.	To assess the bioavailability of celecoxib administered as oral single doses of 200- and 400-mg suspensions relative to 200- and 400-my commercial capsules; to investigate the safety and tolerability of single doses of celecoxib oral suspension versus capsule formulation.	Open-label, randomized, 4-period, 4-treatment, relative bioavailability study of celecoxib commercial capsule and suspension formulations in healthy adult volunteers.	Treatment Group: Single 200 mg and 400 mg celecoxib capsule doses, and 200 mg and 400 mg celecoxib suspension doses at 20 mg/mL with 240 mL water, according to the randomization schedule under fasting conditions on Days 1, 8, 15 and 22.
A3191202 (Study 1202) Total # patients randomized: 24	Healthy adults.	To assess the bioavailability of celecoxib when administered as capsule contents sprinkled on applesauce* relative to capsule administered intact. *Musselman's Applesauce for use in Treatment B.	Open-label, randomized, 2-period, 2-treatment, 2-sequence (AB and BA), single-dose trial in healthy adult volunteers.	Treatment Groups: 100 mg celecoxib intact capsule or content sprinkles. Dose regimen was a single, 100 mg capsule dose. Trial treatments were separated by a washout of at least seven days.
RR-754-00049 (RR 049) Total # patients randomized: 43 adults with RA; 73 patients with JRA (3 mg/kg BID treatment group); 79 patients with JRA (6	Adult patients with rheumatoid arthritis (RA). Patients with JRA (polyarticular, pauciarticular or systemic course JRA).	To characterize celecoxib PK in patients with JRA using a population analysis and identify covariates that are important determinants of celecoxib exposure; to compare the oral	Population pharmacokinetics of celecoxib in patients with JRA studied within the design of the pivotal study 195. (See Study 195 design description above.)	For patients with JRA: treatment groups were the same as described under pivotal Study 195. For adult patients with RA: celecoxib 200 mg BID (400

Protocol #, Study, Total # Patients Randomized	Entry Criteria; Age; Diagnosis	Objective	Study Design	Treatment
mg/kg BID treatment group);		clearance and overall exposure of celecoxib in various age groups of patients with JRA to that of an adult cohort with RA; to explore exposure-response (E-R) relationships using JRA-30 Definition of Improvement (primary efficacy measure) data; and to derive capsule dosing recommendations for patients with JRA after accounting for differences in absorption between capsule and suspension dosage forms of celecoxib.	In parallel, adult patient with RA: 2-week, assigned, open-label multicenter study to evaluate the PK and safety of celecoxib 200 mg BID (400 mg/day) administered as an oral suspension.	mg/day) administered as an oral suspension (100 mg/5 mL strength) for 14 days.
JRA - Juvenile Rheumatoid Arthritis [polyarticular, pauciarticular or systemic course JRA]; RA - rheumatoid arthritis; PK = pharmacokinetics; BID = twice a day; JRA DOI 30 = a core set of outcome measures for assessment of JRA improvement defined as at least 30% improvement from baseline in three of any six variables in the core set, with no more than one of the remaining variables worsened by more than 30%. The six core variables are: 1) investigator global assessment of disease activity; 2) parent/patient global assessment of over-all well0being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) C-reactive protein (CRP).				

4.3 Review Strategy

The NDA pediatric supplement review included four clinical trial study reports and one research report from the pivotal Study 195. The two PK studies are summarized in Section 5.0 Clinical Pharmacology. See the Clinical Pharmacology review by Srikanth Nallani, PhD and Atul Bhattaram, PhD. The Statistics review was completed by Katherine Meaker, PhD. The safety review was conducted from the 12-week double-blind study and the 12-week open-label extension study. The NSAID class label and the CELEBREX (celecoxib) label for adults were relied upon for adverse event comparison.

4.4 Data Quality and Integrity

Quality assurance audits were performed at four centers (01005 [US], 01006 [Peru], 01021 [Peru], and 01035 [US]) by Pfizer's own independent quality assurance group. The sponsor

explains that these audits were conducted according to Pfizer's procedures and Good Clinical Practice (GCP) guidelines.

The Division of Scientific Investigations (DSI) audit process was requested by the Division to inspect two domestic clinical sites. The two clinical sites inspected were: 1) site PH75490 (Principle Investigator: E.C. Chalom at the St. Bomabus Medical Center in Livingston, New Jersey and 2) site 65102 (Principle Investigator: R. F. Rivas-Chacon at Miami children's Hospital in Miami, Florida). These two clinical sites were selected for routine inspection based on the review of the Phase 3 Study 195 protocol violations, errors in prohibited concomitant medications and the total number of patients with JRA who were screened, randomized, enrolled and completed, by clinical center. The Division of Scientific Investigations has verbally reported to the Division of Anesthesia, analgesia and Rheumatology Products that both sites have been found to be acceptable. The formal DSI consult response is pending at this time.

The Case Report forms (CRFs) are acceptable and were utilized in this Medial Officer's review of submitted materials. No special government employees (SGE) were a participant in this review. According to the sponsor, appropriate steps were documented to ensure accurate, consistent and complete data has been used in this submission. All data-entry processing and quality control were performed by Pfizer. These studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

As explained by the sponsor, "a Pfizer monitor or appointed agent monitored the study through routine center visits to discuss the progress of the clinical trial and review CRF data and the original source documents with the study personnel for accuracy of data recording, study drug accountability, and correspondence. The investigator ensured that the trial participants were consented and made aware that personal information could be reviewed during the data verification process as part of monitoring/auditing processes by properly authorized agents of Pfizer or patient to inspection by regulatory authorities. Participation and personal information were treated as confidential to the extent the applicable law permits and were not publicly available."

4.5 Compliance with Good Clinical Practices

The informed consent documents were appropriate for parents and patients, and the documents were age appropriate for pediatric patients who were able to understand their rights. The protocols, revised protocols, and the informed consent form were reviewed and approved by an Institutional Review Board (IRB). The clinical trials were conducted in accordance with acceptable ethical standards for pediatric patients and their families.

4.6 Financial Disclosures

In accordance with 21 CFR Part 54, a signed Form 3455 (Disclosure: *Financial Interests and Arrangements of Clinical Investigations*) was included with this NDA Supplement. According to the sponsor, all of the clinical investigators were noted to have acceptable financial arrangements

with the sponsor as defined in 21 CFR Part 54. There have been no issues raised about the integrity of the data submitted.

5 CLINICAL PHARMACOLOGY

Study 088
This study was an integrated clinical and statistical report for an open label, randomized, single dose, four-way crossover study to examine the pharmacokinetics, dose proportionality and the food effect on the pharmacokinetic profile of 50 mg and 100 mg doses of the commercial formulation of SC-58635 in 24 healthy adult subjects. Under fasting conditions, adult patients appear to show that SC-58635 was readily absorbed, with a Cmax within approximately 2 to 3 hours of dosing. Following the administration of food, Cmax and Tmax and area under the curve (AUC) values were all increased for the dose groups, 50 mg and 100 mg, compared to the fasting conditions. The dose proportionality between the 50 mg and 100 mg doses, under fasting conditions, appeared to be demonstrated for all of the AUC values; however, not for the Cmax values. When the 50 mg and 100 mg SC-58635 doses were administered with food, dose proportionality between the 50 mg and 100 mg SC-58635 doses was achieved for both AUC and Cmax values. In summary, according to the sponsor, the study demonstrated that the administration of food with SC-58635 delayed study drug absorption but also increased mean AUC values (by 7 to 12% in the 50 mg dose group and by 7-20% in the 100 mg dose group).

See Section 4.2, Table 1 Summary of the Studies for the Celecoxib Pediatric Filing.
See the Clinical Pharmacology review by Srikanth Nallani, PhD. and Atul Bhattaram, PhD.

Study 1162
This study was an open-label, randomized, four-period, four-treatment, relative bioavailability study of celecoxib commercial capsule and suspension formulations in 21 healthy adult volunteers who received oral single doses of 200 mg and 400 mg suspensions at 20 mg/mL relative to 200 and 400 mg commercial capsules. Seventeen subjects completed the study. According to the sponsor, based on the mean Cmax, peak celecoxib exposure following 200 and 400 mg suspension doses was less than that observed following the 200 and 400 mg capsule doses. The sponsor states, "… total exposure based on the 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∞)] vales ranged from 84 to 87 % for the suspension doses relative to the capsule."

In conclusion, the maximum celecoxib plasma concentrations following suspension doses appear to be approximately half of the celecoxib peak plasma concentrations observed following the respective capsule doses. This medical reviewer concludes that dosing pediatric patients with a capsule formulation will require caution to avoid potential higher than the proposed celecoxib dosing secondary to higher peak plasma concentrations demonstrated with this formulation as compared to the oral suspension in the smaller weight patients. Clinical pharmacology reports that this observation may pertain only to 10 kg patients. The simulations demonstrate that higher weight categories have plasma concentrations in the range of doses studied and exposures as noted.

Study 1202
This was a relative bioavailability study of celecoxib administered as capsule contents sprinkled on applesauce in 24 healthy adult volunteers conducted as an open label, randomized, two-period, two-treatment, two sequence (AB and BA), single dose trial. The two 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). The trial treatments were separated by a washout of 7 days. All the subjects received both doses of celecoxib and completed the study. As explained by the sponsor, "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 (t½) values were similar for each treatment, averaging approximately 11 hours." Study 1202 indicates that celecoxib as 100 mg capsule can be administered either as an intact capsule or by emptying the contents onto applesauce without altering its' bioavailability. The sponsor concludes that the proposed 50 mg capsule may similarly be administered as an intact capsule or sprinkled over applesauce without altering the bioavailability. The proposed 50 mg capsule was not studied in pediatric patients. See the Clinical Pharmacology review by Srikanth Nallani, PhD and Atul Bhattaram, PhD.

RR-049
This research report (RR) was a population pharmacokinetics study of celecoxib in pediatric patients with JRA. The objective of this study was characterize celecoxib pharmacokinetics in JRA patients using a population analysis and to identify co-variants that are important determinants of celecoxib exposure and to compare the oral clearance and overall exposure of celecoxib in various age groups of JRA patients to that of an adult RA cohort, to explore exposure-response (E-R) relationships using the JRA DOI 30 data; and to derive a capsule dosing recommendation for JRA patients after accounting for the differences in absorption between the capsule and the oral suspension dosage forms of celecoxib. See the Clinical Pharmacology review by Atul Bhattaram, PhD and Srikanth Nallani, PhD.

5.1 Pharmacokinetics

Celecoxib peak plasma levels occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID (400 mg/day); at higher doses there are less than proportional increases in Cmax and AUC. With multiple dosing, steady state conditions are reached on or before Day 5. In healthy adult subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces.

As explained by the sponsor, oral clearance of celecoxib increases less than proportionally with weight in patients with JRA. In Study 195, a 10 kg patient is predicted to have 40% lower clearance (CL/F) compared with a 70 kg adult. See the Clinical Pharmacology review by Srikanth Nallani, PhD. and Atul Bhattaram, PhD for comment on systemic exposures from the

50 mg capsule formulation of celecoxib in JRA patients within the current labeled doses (100 mg to 200 mg BID capsule) in adult RA patients.

5.2 Pharmacodynamics

See the Clinical Pharmacology review by Srikanth Nallani, PhD and Atul Bhattaram, PhD.

5.3 Exposure-Response Relationships

In the double-blind phase of Study 195, patients in the low-dose celecoxib and high-dose celecoxib treatment groups received less than the pre-specified dose in the two study medication treatment arms: 51% (39/77) patients in the low-dose celecoxib group and 57% (47/82) patients in the high-dose celecoxib group, received < 5 mg/kg/day and < 10 mg/kg/day, respectively. In the open-label phase, 31% (63/202) patients in the single high-dose celecoxib group received < 10 mg/kg/day. The sponsor explained that the study treatment arms would target a low-dose and a high-dose based on patient body weight. With consideration of the under-dosing in the celecoxib groups, in the double-blind and open-label phases, the exposure-response data submitted for low-dose celecoxib and high-dose-celecoxib demonstrated non-inferiority to naproxen suspension (15 mg/kg/day) by the primary efficacy endpoint of the JRA DOI 30.

See Section 6.0 Efficacy Findings for details of the response by the JRA DOI 30, exposure as pre-specified and non-pre-specified sub-analysis of the exposed patients according to the sponsor's proposed dosage and administration.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the relief of signs and symptoms of juvenile rheumatoid arthritis (JRA) for patients greater than or equal to two years of age (b) (4) with (either polyarticular, pauciarticular or systemic course) JRA. There are no other indications sought by the sponsor from this pediatric efficacy and safety supplement.

6.1.1 Methods

Clinical data was received from the pivotal Phase 3 efficacy and safety study N49-01-01-195 (Study 195), designed as a 12-week, randomized, double-blind, non-inferiority, multicenter, active-controlled, parallel group study to evaluate the safety and efficacy of celecoxib investigational oral suspension at target dosages of 3 mg/kg BID (6 mg/kg/day) and 6 mg/kg BID (12 mg/kg/day) compared to naproxen oral suspension at a target dosage of 7.5 mg/kg BID (15 mg/kg/day) for the treatment of the signs and symptoms of pauciarticular, polyarticular, and systemic-onset (with currently inactive features) of JRA. This study was conducted in patients with JRA who were greater than or equal to two years of age up to less than or equal to 16 years

of age, and was conducted in 61 clinical centers across 16 countries (Belgium, Brazil, Canada, Denmark, France, Germany, Mexico, Norway, Peru, Portugal, Russian Federation, Solvakia, Slovenia, Spain, Sweden, and the United States). There were 3 patients who had reached their 17th birthday included in this study. See **Appendix 10.1** Protocol for Study 195.

6.1.2 General Discussion of Endpoints

Primary Efficacy Endpoint
The primary endpoint for evaluating efficacy in the double-blind phase and in the open-label extension phase of Study 195 was the proportion of patients meeting the criteria of the Juvenile Rheumatoid Arthritis Definition of Improvement greater than or equal to 30 % (JRA DOI 30). The JRA DOI 30 criterion is defined as achieving at least 30 % improvement from baseline in any of three of six core variables, with no more than one of the remaining variables worsening by greater than 30 %. The 6 core variables of the JRA DOI 30 are as follows: 1) Investigator's global assessment of disease activity (score of at least 10 mm on a 100-mm Visual analogue Scale [VAS] at screening); 2) Parent/Patient's Global Assessment of Well-Being (score of at least 10 mm on a 100-mm VAS); 3) Functional Ability (measured by the Child Health Assessment questionnaire; 4) Number of Joints with Active Arthritis; 5) Number of Joints with Limited Range of Motion; and 6) C-reactive Protein. Efficacy was examined in patients ≥ 2 years of age to ≤ 16 years of age.

The development of this primary efficacy endpoint was a multi-step process initiated in 1993 with an advisory council consisting of members of the Rheumatology Section of the American Academy of Pediatrics (AAP), the Pediatric Section of the American College of Rheumatology (ACR), and the Arthritis Foundation, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) participants, and private and academic practitioners. The OMERACT project led to the development of the ACR core set and definition of improvement (ACR20) used in adult rheumatoid arthritis (RA) and has since been endorsed by the World Health Organization and the International League Against Rheumatism (ILAR).[1]

The performance characteristics (validity, reliability, and sensitivity to change, redundancy) of all variables that received votes in the survey questionnaire were investigated using the literature and the core data bank of the Pediatric Rheumatology Collaborative Study Group (PRCSG) which contained all data from all trials of second line agents studied by the PRCGS. Through additional conferences from 1994 through 1996, the definition of improvement that scored the highest was as follows: at least 30 % improvement in at least three core set variables, with no more than one of the remaining variables deteriorating by more than 30%. Patients should be evaluated as improved or not improved by comparing the values of the core end points at the end of the trial, or at withdrawal from the trial (intent-to-treat approach).[1] Due to the lack of widely available laboratory markers of inflammation in children and adolescents with juvenile rheumatoid arthritis, the erythrocyte sedimentation rate (ESR) was initially used as a biomarker of response. The C-reactive protein (CRP) is now used more often as a biomarker of inflammation in juvenile rheumatoid arthritis.[2]

The primary endpoint, Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30 % (JRA DOI 30), is robust enough to cover the three clinical types of JRA (pauciarticular, polyarticular and systemic course), focusing on the key features of arthritis, function, and overall well-being. The JRA DOI 30 has greater than 80% sensitivity and specificity, and high face validity.

The JRA DOI 30 endpoint has six core variables that apply to all three subtypes of JRA. The definition of improvement is biased toward joint counts (2/6 core variable components), which could potentially limit its' usefulness in the assessment of pauciarticular disease (patients with less than or equal to four joints). In addition, the definition of improvement does not include an assessment of pain relief. The Childhood Health Assessment Questionnaire* contains two of 69 parameters that, specifically, focus on pain.

In the statistical analysis plan, the efficacy portion of the primary objective of Study 195 was addressed by the primary analysis of the JRA DOI 30. The non-inferiority of the celecoxib oral suspension to the naproxen oral suspension in treating the signs and symptoms of JRA was evaluated using the 95% 2-sided binomial confidence intervals (CI) for the difference in the percent improved patients, as defined by the JRA-30 DOI criterion at Weeks 2, 4, 8, and 12 (Final visit). Non-inferiority of celecoxib was claimed if the lower limit of the 95% 2-sided CI for the difference in the percent responders (celecoxib-naproxen) was above -25%. The primary endpoint was the Week 12 time point. Pair-wise treatment comparisons using the Chi-Squared test were performed for the three treatment groups with regard to the proportion of JRA DOI 30 responders, at Week 2, 4, 8, and 12 (Final visit)

References:
1. Giannini EH, Ruperto N, Ravell A et al: Preliminary definition of improvement in juvenile arthritis. Arth Rheum 40:1202-1208, 1997.
2. Giannini EH, Brewer EJ: Poor correlation between the erythrocyte sedimentation rate and clinical activity in juvenile rheumatoid arthritis. Clin Rheum 6:197-201, 1987.

Secondary Efficacy Endpoints
The secondary efficacy evaluations in Study 195 were the Parent's Assessment of the Child's Arthritis Pain (visual analogue scale [VAS]) (CHAQ* subsection) and the Pediatric quality of Life Inventory, as well as various definitions of improvement for use in the JRA population (JRA-50 DOI, JRA-70 DOI, and the JRA-30 DOI in pauciarticular and polyarticular course JRA, separately).

The change from Baseline at each visit was analyzed for the Physician's Global Assessment of Disease Activity, the Parent's Global Assessment of Overall Well Being (CHAQ subsection), Parent's Assessment of Physical Function (CHAQ Disability Index), the Parent's Assessment of Child's Arthritis Pain (VAS) (CHAQ subsection), the number of joints with active arthritis, the number of swollen and tender/painful joints assessed separately, number of joints with limited range of motion, CRP, and the Pediatric Quality of Life Health-related Quality of Life (PedsQL^{TM}). These analyses were carried out using an Analysis of Covariance (ANCOVA) model including terms for treatment group, protocol stratum, joint involvement stratum (pauciarticular, polyarticular and systemic course JRA), age group, and weight group as the

factors and Baseline values as a 1-degree-of-freedom covariate. The last assessment of improvement was carried forward if a subject withdrew prior to the final visit at 12 weeks.

Exploratory Endpoints
Post-hoc analyses were performed separately by the sponsor for the percentage of patients with either pauciarticular or polyarticular JRA for the JRA DOI 30 criterion. Post-hoc analyses were also performed separately for the percentage of patients who met either the JRA DOI 50 criterion or the JRA DOI 70 criterion.

Analysis of Pharmacokinetic Parameters
The sponsor explained that "nonlinear mixed effects modeling (NONMED) methodologies were used to develop a population PK model for celecoxib plasma concentrations in the JRA and adult RA patient populations. Celecoxib concentrations were modeled with a 1-compartment model with first-order absorption. Within-patient variability was modeled with an additive error on the log-transformed concentration. Inter-individual variability in the PK parameters (oral clearance [CL/F] and volume [V/F]) was modeled using exponential random effects." As noted by the sponsor, "covariates were added to the base model simultaneously to form the full model."

6.1.3 Study Design

The pivotal Study 195 was a 12-week, randomized, multicenter, double-blind, active-controlled parallel group study to evaluate the efficacy and safety of a low-dose and a high-dose of celecoxib oral suspension compared to naproxen oral suspension in patients with JRA. This study was conducted in both domestic and non-domestic clinical centers. The study design and protocol was finalized though multiple discussions and meetings with the Agency and is presented in **Appendix 10.1** of this supplement review.

6.1.4 Efficacy Findings

EFFICACY FINDINGS
Study 195

In Study 195, the Phase 3, 12-week study, a low-dose of celecoxib oral suspension as 6 mg/kg/ day (3 mg/kg BID) as 50 mg/5 mL and a high-dose of celecoxib oral suspension as 12mg/kg/day (6 mg/kg BID) as 100 mg/5 mL were tested in patients with JRA. Naproxen oral suspension was selected as the active comparator and administered as 15 mg/kg/ day (7.5 mg/kg BID) as a 125 mg/5 mL oral suspension. Eligible patients who met all the inclusion and exclusion criteria for the study underwent a washout of NSAID therapy defined as a timeframe greater than five half-lives or a minimum of 48 hours of prior NSAID therapy, whichever was greater. Patients discontinued rofecoxib*, oxaprozin, and or piroxicam four days prior to the Baseline visit. NSAIDs were prohibited during study participation.

Patients with JRA were then randomly assigned to one of three treatment groups in approximate equal proportions: 1) celecoxib low-dose oral suspension, 6 mg/kg/day, target dose of 3 mg/kg/ day twice daily [BID] as 50 mg/5 mL; 2) celecoxib high-dose oral suspension, 12 mg/kg/day, target dose of 6 mg/kg BID as 100 mg/5 mL; or 3) naproxen oral suspension, 15 mg/kg/day,

target dose of 7.5 mg/kg BID as 125 mg/5 mL, in a 1:1:1 ratio. The volume of study medication administered was determined by the patient's total body weight at the Baseline visit. Study medication was taken BID before breakfast and before bedtime. Stable DMARD therapies were permitted but only if the doses were anticipated to remain unchanged over the study course.

The allocation of the double-blind study drug dispensing to patients with JRA is described in Table 2. The sponsor explained that the patient's dosing was not changed during participation in the double-blind phase of the study, even if the patient's weight subsequently changed. This approach to patient weight during the double-blind and/or the open-label was not an issue in Study 195. Allocations in the treatment arms were stratified by JRA course type (e.g., pauciarticular and polyarticular joint involvement or systemic onset JRA with inactive systemic features) to obtain approximate equal numbers of patients. Approximately 10% of the patients included in Study 195 had systemic onset of JRA.

Those patients who elected to enter the optional open-label extension phase of Study 195 received high-dose celecoxib oral suspension, 12 mg/kg/day as 100 mg/5 mL oral suspension for 12 weeks. The volume of open-label study medication administered was determined by the patient's weight at the Week 12 visit/final visit of the double-blind phase. The 12-week extension study was designed to investigate chronic administration of celecoxib for tolerability and durability in patients ≥ 2 to 16 years of age.

**Note: Study 195 was initiated October 16, 2002 and the last patient visit was April 11, 2005. This study period briefly includes the approval of VIOXX (rofecoxib), a NSAID/COX-2 selective inhibitor, for patients with polyarticular and pauciarticular JRA [August 18, 2004] Merck voluntarily withdrew rofecoxib from the global market [September 30, 2004] for cardiovascular safety reasons.*

Table 2. Volume of Study Medication Administered to Patients with JRA (Study 195)
(Sponsor Table 4, page 42 of 4701.)

Patient Weight	Bottle A	Bottle B
9-12 kg	2.5 mL	2.5 mL
13-25 kg	5 mL	5 mL
26-37 kg	7.5 mL	7.5 mL
38-50 kg	10 mL	10 mL
> 50 kg	15 mL	20 mL
Abbreviations: kg = Kilogram; mL = Milliliter		

Follow up clinical assessments were performed at Weeks 2, 4, 8, and 12 during the double-blind phase of Study 195. A treatment effect was observed from Weeks 12 to 24 (visits at Week 12, 16 and 24) for patients who enrolled in the open-label extension treatment phase of Study 195 with high-dose celecoxib 12 mg/kg/day, 6 mg/kg BID. The adults with rheumatoid arthritis were assigned to a single treatment group where celecoxib suspension 200 mg (100 mg/5 mL for a total of 10 mL per dose) was administered BID (400 mg/day) for 14 days.

Patient Disposition
Juvenile Patient Disposition

Of the 242 patients with JRA allocated at the randomization visit (Visit 1), all 242 patients with JRA received at least one dose of study medication. Of the 242 randomized patients with JRA, 212 completed the double-blind phase of Study 195. There were 30 patients who did not complete the double-blind phase of Study 195. Overall, 4 (5%), 7 (9%) and 4 (5%) patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, withdrew secondary to adverse events; 2 (2.6%), 1 (1.2%) and 4 (4.8%) in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, withdrew due to lack of efficacy. Protocol violation, consent withdrawn, and lost to follow-up comprise the categories that describe the circumstances for the remainder of the 30 patients who did not complete the double-blind phase. See Table 3.

Two-hundred and twelve (87.6%) patients with JRA completed the double-blind phase. There were 10 (4.1%) patients who elected not to enter the open-label extension phase of Study 195. Consent withdrawal was reported as 3 (3.9%), 1 (1.2%) and 3 (3.6%) patients in the low-dose celecoxib, high-dose celecoxib and naproxen, respectively. Protocol violation, lack of efficacy, and sponsor decision comprise the categories for the remainder of the 10 patients who did not elect to enter the open-label phase.

Two-hundred and two JRA patients enrolled in the open-label phase and 195 (96.5%) patients completed this phase. Overall, the three most common reasons for early withdrawal were an adverse event, 1 (1.6%), 1 (1%) and 1 (1.4%) in the low-dose celecoxib, high-dose celecoxib and naproxen groups, respectively; protocol violation was reported in 1 (1.6%), 1 (1.6%) and 0 (0.0%) patients in the low-dose celecoxib, high-dose celecoxib and naproxen, respectively; and consent withdrawn was reported in 0 (0.0%), 2 (2.9%) and 0 (0.0%) patients in the low-dose celecoxib, high-dose celecoxib and naproxen groups, respectively. See Table 3.

Table 3. JRA Patient Disposition: Double-Blind and Open-Label Phases (Study 195)
(Developed from Sponsor Table B, page 28 of 4701)

	Celecoxib 6 mg/kg/day (3 mg/kg BID)	Celecoxib 12 mg/kg/day (6 mg/kg BID)	Naproxen 15 mg/kg/day (7.5 mg/kg BID)	Total
Randomized to DB Phase	77 (100%)	82 (100%)	83 (100%)	242 (100%)
Completed DB Phase	67 (87%)	71 (87%)	74 (89%)	212 (88%
Early Withdrawal During DB Phase	10 (13%)	11 (15%)	9 (11%)	30 (12%)
Reason for Withdrawn				
Adverse Event	4 (5%)	7 (9%)	4 (5%)	15 (6%)
Protocol violation	0 (0%)	1 (1%)	1 (1%)	2 (1%)
Consent Withdrawn	4 (5%)	2 (2%)	1 (1%)	7 (3%)
Lost to Follow-Up	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Lack of Efficacy	2 (3%)	1 (1%)	4 (5%)	7 (3%)
Completed DB Phase; Did not	5 (7%)	1 (1%)	4 (5%)	10 (4%)

Enter OL Phase				
Reason for Not Entering OL Phase				
Protocol violation	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Consent Withdrawn	3 (4%)	(1%)	3 (4%)	7 (3%)
Lack of Efficacy	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Sponsor's Decision	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Enrolled in OL Phase/ Med Taken	62 (100%)	70 (100%)	70 (100%)	202 (100%)
Completed OL Phase	60 (97%)	66 (94%)	69 (99%)	195 (97%)
Early Withdrawal During OL Phase	2 (3%)	4 (6%)	1 (1%)	7 (4%)
Adverse Event	1 (2%)	1* (1%)	1 (1%)	3 (2%)
Protocol Violation	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Consent Withdrawn	0 (0%)	2 (3%)	0 (0%)	2 (1%)
Protocol Specific Withdrawal Criteria	0 (0%)	1 (1%)	0 (0%)	1 (1%)
* Pt 1044 had sJRA. The discrepancy in this reviewer's number of AEs in the low dose celecoxib group and the naproxen group differ from the sponsor's because the sponsor considered these AEs as protocol criteria for withdrawal rather than AEs. Abbreviations: DB=double-blind; OL=open-label.				

Adult Patient Disposition

The adult treatment group with RA participated in a two-week, assigned open-label population PK study performed as part of Study 195. The PK profile of celecoxib suspension was compared in children and adolescents with JRA to the PK profile in the adult treatment group who took celecoxib 200 mg BID, 400 mg/day, (100 mg/5 mL suspension) for 14 days. Of the 43 adult patients with RA enrolled in Study 195, 5 experienced adverse events (12%). Two adult patients experiencing adverse events were withdrawn from the study. One additional patient withdrew secondary to a protocol violation. See Section 6.0, Safety, of this review.

Demographics and Other Baseline Characteristics

Overall, the 242 juvenile patients randomized across the three treatment groups in Study 195 were comparable at Baseline ($p > 0.05$) in the double-blind phase with respect to the variables of age, gender, race, height, weight, and were balanced with respect to duration of JRA, the presence of polyarticular or pauciarticular JRA, and the onset of systemic features of JRA.

Age, Juvenile

The patients' ages ranged from ≥ 2 years to ≤ 17 years of age. The sponsor states that no patients had reached their 17th birthday at the Baseline visit. **This medical reviewer noted that there were 3 patients reported as 17 years of age at Baseline.** One hundred and sixty-nine (69.8%) where less than or equal to 12 years of age and 73 (30.1%) were equal to or greater than 13 years of age. The mean age of patients in the three treatment arms were 10.44 years, 10.16 years and 10.39 years, in the celecoxib low dose, celecoxib high dose, and naproxen treatment groups, respectively. Thirty-nine patients were between two years and four years of age. Sixteen percent of the total randomized patients were equal to or less than four years of age. See Table 4.

Age, Adult
In the adult patient population with RA (n = 43), the mean age was 52.79 years and a median age of 52.3 years. All enrolled patients with RA were Caucasian and 63% were women. See Table 5 for the age and other demographic characteristics of the adult patients enrolled in Study 195.

Sex
Of the 242 randomized patients, 171 (70.6 %) were female and 71 (29.3 %) were male. This balance of females to males is consistent with the incidence of JRA disease by subtypes, poly-articular and pauciarticular JRA, having a higher incidence in females than in males. The majority of the adult patients were women. See Table 4.

Racial and Ethnic Background
Of the 242 randomized patients, 145 (58 %) were Caucasian, 20 (8 %) were black, five were Asian (2%), and 77 (32 %) patients were not designated by race in the Case Report Forms (CRF). See Table 4.

Weight
Among the 242 patients aged 2 to 17 years of age, the mean weight and range across the three treatment groups was 36.2 kg (12.2 to 68.0 kg), 36.2 kg (10.6 to 92.7 kg), and 37.3 kg (13.0 to 79.0 kg) in the celecoxib low-dose treatment group, celecoxib high-dose treatment group and the naproxen treatment group, respectively. The weight criterion was amended (lowered) in the protocol from 15 kg to 9 kg to be consistent with the typical weight range of smaller weight children and to enhance recruitment of younger and smaller weight children.

Among the 77 patients in the low-dose celecoxib treatment group, there were 20 patients who weighed greater than or equal to 50 kg, 10 to 16 years of age, and there were 57 patients who weighed less than 50 kg, 9 to 2 years of age. Among the 82 patients in the high-dose celecoxib treatment group, there were 17 patients who weighed greater than or equal to 50 kg, 9.4 years to 17 years of age, and there were 65 patients who weighed less than 50 kg, 8 to 2 years of age. See Table 4.

Table 4. Demographics and Patient Baseline Characteristics of All Juvenile Randomized Patients
(From Sponsor Table 15, page 69 of 4701)

	Celecoxib 6 mg/kg/day N=77	Celecoxib 12 mg/kg/day N=82	Naproxen 15 mg/kg/day N=83
Age (yrs): Mean	10 (4%)	10 (4%)	10 (4%)
Distribution by Age Category N (%)			
2-4 yrs	13 (17%)	16 (20%)	10 (12%)
5-7 yrs	9 (12%)	9 (11%)	11 (13%)
8-12 yrs	31 (40%)	35 (43%)	35 (42%)
13-16 yrs	24 (31%)	22 (27%)	27 (33%)
Gender N (%)			
Female	59 (77%)	53 (65%)	59 (71%)
Male	18 (23%)	29 (35%)	24 (29%)
Race N (%)			

White	41 (53%)	47 (57%)	52 (63%)
Black	9 (12%)	7 (9%)	4 (5%)
Asian	1 (1%)	3 (4%)	1 (1%)
Not Listed	36 (34%)	25 (31%)	26 (31%)
Height [a] (cm)	137 (22%)	135 (24%)	138 (22%)
Weight [a] (kg)	36 (16%)	36 (18%)	37 (16%)
Duration of JRA (yrs): Mean (SD)	3 (3)	4 (3)	3 (3)
Onset with Systemic Features N (%)	4 (5%)	10 (12%)	8 (10%)
Course N (%)			
Pauciarticular	37 (48%)	45 (55%)	46 (55%)
Polyarticular	40 (52%)	37 (45%)	37 (45%)

Table 5. Adult Patients with RA in Study 195
(Developed from Sponsor Table T3.3, page 130 of 4701)

	Celecoxib Suspension, 200 mg BID (N = 43)
Age in Years	
Mean	52.79
Range	18.90 – 83.20
Gender	
Female	27 (62.8%)
Male	16 (37.2%)
Race / Ethnic Origin	
Caucasian	43 (100 %)
Black, Asian, not listed in CRF	0 (0.0%)

JRA Sub-types

The JRA sub-types, pauciarticular and polyarticular course, were well-balanced in across the three treatment arms. There were 128 (52%) patients with pauciarticular course JRA, and 114 (47%) patients with polyarticular course JRA. There were 22 patients (9%) studied whose JRA disease onset included systemic features: 4 (5.2 %) in the low-dose celecoxib group, 10 (12 %) in the high-dose celecoxib group and 8 (10 %) the naproxen treatment group. Patients with systemic onset JRA, but without active systemic features at randomization, were included in this study to investigate the efficacy and safety profile of non-selective NSAID/COX-2 selective inhibitors in this subset of JRA patients.

Secondary Diagnoses

Juvenile Rheumatoid Arthritis Patients

The most common secondary diagnoses in Study 195 are reported by treatment group in Tables 6, 7, and 8. Anemia was the most common secondary diagnoses in the low-dose celecoxib treatment group. Asthma, cardiac murmur, osteoporosis, hyperlipidemia and uveitis occurred in 4 or fewer patients in this cohort. Gastroduodenal ulcer had occurred in 1 patient in the past. Asthma and anemia were the most common secondary diagnoses in the high-dose celecoxib treatment group. Calculus in the kidney/ureter, cardiac murmur, uveitis, iritis, diabetes mellitus, hematuria, and valvular heart disease occurred in 4 or fewer patients. There was 1 patient with a past history of hypertension.

Anemia and asthma were the most common secondary diagnoses in the naproxen treatment group. Calculus of the kidney/ureter, cardiac murmur, diabetes, osteoporosis, and uveitis occurred in 6 or fewer patients. Hematuria and valvular heart disease, each in separate patients, occurred as an active secondary diagnosis in the naproxen treatment group.

Table 6. Secondary Diagnoses, Randomized JRA Patients (celecoxib 6 mg/kg/day group)

JRA Treatment Group		Status of Secondary Diagnosis at Randomization			
Celecoxib Suspension 3 mg/kg BID	Secondary Diagnosis	Active Diagnosis	Controlled Diagnosis	Past Diagnosis, Resolved	Total # Pts. with Active and/or Controlled Secondary Diagnosis
	Anemia	6	7	5	13
	Asthma	1	3	3	4
	Cardiac Murmur	1	3	1	4
	Gastroduodenal Ulcer	0	0	1	0
	Hyperlipidemia	0	1	1	1
	Osteoporosis	2	2	0	4
	Uveitis	1	0	1	1

Table 7. Secondary Diagnoses, Randomized JRA Patients (celecoxib 12 mg/kg/day group)

JRA Treatment Group		Status of Secondary Diagnosis at Randomization			
Celecoxib Suspension 6 mg/kg BID	Secondary Diagnoses	Active Diagnosis	Controlled Diagnosis	Past Diagnosis, Resolved	Total # Pts. with Active and/or Controlled Secondary Diagnosis
	Anemia	8	3	10	11
	Asthma	0	6	3	6
	Calculus in Kidney/Ureter		1		1
	Cardiac Murmur	3	1	1	4
	Diabetes Mellitus	0	1	0	1
	Hematuria	1	0	1	1
	Hypertension	0	0	1	1
	Iritis	0	0	2	2
	Osteoporosis	0	1	0	1
	Uveitis	3	1	1	4
	Valvular Heart Disease	1	0	0	1

Table 8. Secondary Diagnoses, Randomized JRA Patients (Naproxen 15 mg/kg/day group)

JRA Treatment Group		Status of Secondary Diagnosis at Randomization			
Naproxen Suspension	Secondary Diagnosis	Active Diagnosis	Controlled Diagnosis	Past Diagnosis, Resolved	Total # Pts. with Active or

125 mg/kg BID					Controlled Secondary Diagnoses
	Anemia	8	3	10	11
	Asthma	0	6	3	6
	Calculus in Kidney/Ureter		1		1
	Cardiac Murmur	3	1	1	4
	Diabetes Mellitus	0	1	0	1
	Hematuria	1	0	1	1
	Hypertension	0	0	1	1
	Iritis	0	0	2	2
	Osteoporosis	0	1	0	1
	Uveitis	3	1	1	4
	Valvular Heart Disease	1	0	0	1

Secondary Diagnoses

Adult RA Patients

Among the adult patients with RA enrolled in the population pharmacokinetic portion of Study 195, cardiac murmur, hyperlipidemia, osteoporosis, and peripheral edema were the most common secondary diagnoses at study enrollment. Anemia, angina (controlled), coronary artery disease (controlled), hypertension (controlled), and valvular heart disease (controlled) occurred in 3 or fewer patients. Renal insufficiency was described as active in 1 patient. See Table 9.

Table 9. Secondary Diagnoses, Adult RA Patients (celecoxib 400 mg/day group)

Adult RA Treatment Group		Status of Secondary Diagnosis at Randomization			
Celecoxib suspension 200 mg BID	Secondary Diagnosis	Active	Controlled	Past Diagnosis, Resolved	Total # Pts. w/ Active or Controlled Secondary Diagnoses
	Anemia	1	1	6	2
	Angina	0	1	0	1
	Asthma	0	1	1	1
	Calculus in Kidney/Ureter	0	0	4	0
	Cardiac Murmur	0	5	0	5
	Coronary Artery Disease	0	1	0	1
	Hematuria	0	0	2	0
	Hyperlipidemia	2	3	2	5
	Hypertension	0	3	2	3
	Renal Insufficiency	1	0	0	1
	Osteoporosis	5	3	0	8
	Peripheral Edema	5	2	1	7
	Valvular Heart	0	1	0	1

	Disease				

Compliance
Of the 242 patients randomized in the double-blind phase, 212 (87.6 %) patients completed the 12-week, double-blind phase. Across the three treatment groups (celecoxib 6 mg/kg/day, 50 mg/ 5mL; celecoxib 12 mg/kg/day, 100 mg/5 mL; and naproxen 15 mg/kg/day, 125 mg/5 mL) in the 12-week, double-blind phase, 87 %, 87 % and 89 % completed the trial in the low-dose celecoxib, high-dose celecoxib and the naproxen treatment groups, respectively.

A total of 202 juvenile patients enrolled in the open-label extension phase and 96.5 % of these patients completed this additional 12-week phase. In the open label phase, 62 patients from the low-dose celecoxib group entered the high-dose celecoxib group; 70 patients continued to receive high-dose celecoxib and 70 patients in the naproxen group entered the high-dose celecoxib treatment group. See the **Appendix 10.1** for the definition of compliance in the protocol.

Prior and Concomitant Medications
The sponsor allowed patients to continue receiving standard of care therapy throughout the trial, provided that the therapy was a stable dose at the study entry and the dose did not change throughout the study. See **Appendix 10.1** for the concomitant medications and prior medications permitted in Study 195.

Of the 242 randomized patients, 39 (51%), 40 (49%) and 43 (52%) of the low-dose celecoxib group, high-dose celecoxib group and naproxen group, respectively, took at least one medication as a DMARD and or a biologic response modifier (BRM) in addition to the study drug during the 12-week double-blind phase. As described in Table 10, the number of patients who were receiving a DMARD, BRM or combination therapy at Baseline was similar across the three treatment groups.

The methotrexate allowable dose was raised to 1 mg/kg/day (up to a maximum allowable dose of 40 mg/week) as a protocol amendment. The rationale for this increase was to be consistent with current clinical practice.

The number of patients who were receiving oral corticosteroids at Baseline was 13 (17%), 16 (20%), and 22 (27%) for the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively. See Table 10.

Table 10. Baseline Anti-rheumatic Medications (DMARDS and or BRM) in Study 195
(Sponsor Table 16, page 70 of 4701)

	Celecoxib 3 mg/kg BID N = 77		Celecoxib 6 mg/kg BID N = 82		Naproxen 7.5 mg/kg BID N = 83	
DMARD/BRM N (%)						
No	38	(49.4)	42	(51.2)	40	(48.2)
Yes	39	(50.6)	40	(48.8)	43	(51.8)
DMARD N (%)						
Azathioprine	0	(0.0)	1	(1.2)	0	(0.0)
Hydroxychloroquine Sulfate	3	(3.9)	2	(2.4)	5	(6.0)
Methotrexate	30	(39.0)	29	(35.4)	28	(33.7)
Sulfasalazine	1	(1.3)	3	(3.7)	3	(3.6)
BRM N (%)						
Etanercept	0	(0.0)	1	(1.2)	0	(0.0)
COMBINATION THERAPY N (%)						
Azathioprine/Infliximab	0	(0.0)	0	(0.0)	1	(1.2)
Methotrexate/Hydroxychloroquine	3	(3.9)	2	(2.4)	2	(2.4)
Methotrexate/Sulfasalazine	0	(0.0)	0	(0.0)	1	(1.2)
Methotrexate/Etanercept	2	(2.6)	0	(0.0)	1	(1.2)
Methotrexate/Infliximab	0	(0.0)	2	(2.4)	1	(1.2)
Methotrexate/Hydroxychloroquine/Sulfasalazine	0	(0.0)	0	(0.0)	1	(1.2)
ORAL CORTICOSTEROIDS N (%)						
No	64	(83.1)	66	(80.5)	61	(73.5)
Yes	13	(16.9)	16	(19.5)	22	(26.5)

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: DMARD = Disease Modifying Anti-Rheumatic Drug; BRM = Biologic Response Modifier.
Source: Section 13; Table T3.2.1

Abbreviations: DMARD=disease modifying anti-rheumatic drug; BRM=biologic response modifier.

Protocol Violations / Deviations

There were 13 JRA patients and 5 RA patients who had protocol inclusion/ exclusion criterion violations. See Table 11. As noted by the sponsor and this medical reviewer, the most commonly occurring protocol violation was the use of prohibited concomitant medication, followed by analgesic medication exceeding the 3-day limit, and noncompliance with study medication. Juvenile or adult patients who deviated from the protocol of Study 195 were excluded, as appropriate, from the analyses of efficacy and safety. All patients who violated the protocol in predefined, significant ways were excluded from the intent-to-treat (ITT) analysis and post hoc analysis.

Use of Prohibited Concomitant Mediation

- ***Naproxen 15 mg/kg/day (125 mg/5 mL) Treatment Group***

There were 4 patients in the naproxen treatment group who took prohibited concomitant medication. Three (3) patients (1193, 1090, and 1105) took a NSAID, piroxicam, metamizole, and metamizole, respectively. One patient (1057) took a proton-pump inhibitor (esomeprazole).

- ***Celecoxib 6 mg/kg/day (50 mg/5 mL) Treatment Group***

There were 7 patients (1047, 1171, 1086, 1088, 1224, 1091, and 1148) in the celecoxib 6 mg/kg/day (50 mg/5mL) treatment group who took a NSAID, specifically, metamizole for the first four patients, etodolac for the fifth patient, and ibuprofen for the last patient, respectively.

- ***Celecoxib 12 mg/kg/day (100 mg/5 mL) Treatment Group***

There were 8 patients in the high-dose celecoxib 12 mg/kg/day (100 mg/ 5mL) treatment group who took prohibited concomitant mediation. One patient (1326) took a proton-pump inhibitor (omeprazole), one patient (1121) took acetaminophen for the relief of arthritis symptoms, one patient (1176) took corticosteroids, and five patients (5013, 5016, 5019, 1032, and 1058) took NSAIDs, naproxen, naproxen, aspirin, diclofencac, and ibuprofen, respectively.

Analgesic Medication Exceeding the 3-Day Limit

- ***Naproxen 15 mg/kg/day (125 mg/5 mL) Treatment Group***

There were 5 patients in the naproxen treatment group who exceeded the allowable analgesic usage: 4 patients (1260, 1117, 1014, and 1151) took acetaminophen 157 days, an unspecified number of days (without a stop date given), 7 days, and 71 days, respectively. There was 1 patient (1193) who took paracetomal 26 days during Study 195.

- ***Celecoxib 6 mg/kg/day (50 mg/5 mL) Treatment Group***

There were 6 patients in the low-dose celecoxib 6 mg/kg/day (50 mg/5 mL) treatment group who took analgesic medication longer than 3 days. Four patients (1351, 1115, 1337, and 1039) took acetaminophen for 9 days, 11 days, 10 days and 4 days, respectively. One patient (1142) took Alka Seltzer Cold 6 days and one patient (1147) took Tylenol #3 for 91 days.

- ***Celecoxib 12 mg/kg/day (100 mg/5 mL) Treatment Group***

There were 7 patients in the high-dose celecoxib 12 mg/kg/day (100 mg/5 mL) treatment group who took analgesic mediation beyond 3 days. Five (5) patients (1338, 1128, 1002 and 1147) took acetaminophen 5 days, for an unspecified number of days (without a stop date given), 102 days and 5 days, respectively. One (1) patient (1164) took Excedrin Quicktabs and Tylenol Jr. Strength for an unspecified time frame (without a stop date given); 1 patient (1019) took Dayquil for 7 days, and another patient (1002) took Tylenol Plus for 4 days.

Non-Compliance with Study Medication

- ***Naproxen 15 mg/kg/day (125 mg/5 mL) Treatment Group***

There were 7 patients in the naproxen treatment group who were reported to be non-compliant. One patient (1149) required withdrawal from Study 195 secondary to non-compliance; two patients (1177 and 1247) were less than 80 % compliant with study medication, a fourth patient (1355) was non-compliant from Week 4 to Week 8 and a fifth patient (1068) was non-compliant from Week 12 to 16. There were two additional patients who received more than the prescribed amount of naproxen: one patient (1288) received twice the prescribed dosage of naproxen between Week 12 to 16, and another patient (1140) received no naproxen from Bottle B from the Baseline visit to an unspecified time.

- ***Celecoxib 6 mg/kg/day (50 mg/5 mL) Treatment Group***

There were 6 patients in the celecoxib 6 mg/kg/day (50 mg/5 mL) treatment group who were reported to be non-compliant with celecoxib. One (1) patient required withdrawal from Study 195 due to non-compliance, one patient was less than 80% compliant at Week 8, and a second patient non-compliant without a percentage of non-compliance specified. A fourth patient missed 8 concurrent days of celecoxib 50mg/5 mL suspension and a fifth patient received half the prescribed celecoxib 50 mg/5 mL dose for 15 days following the Baseline visit. There was 1

patient who intentionally took more than the prescribed number of doses of celecoxib 6 mg/kg/day (50 mg/5 mL) oral suspension.

- ***Celecoxib 12 mg/kg/day (100 mg/5 mL) Treatment Group***

There were 5 patients in the high-dose celecoxib 12 mg/kg/day (100 mg/5 mL) treatment group who were reported as non-compliant. None of these patients required withdrawal from Study 195. Two patients were less than 80% compliant with high-dose celecoxib 12 mg/kg/day (100 mg/ 5 mL), 1 patient (# 1338) between Weeks 12 and 16, and the other patient (1271) non-compliant from Week 4 to Week 8 and also from Week 12 and 24. Another patient (# 1169) received half the prescribed dosage of high-dose celecoxib 12 mg/kg/day (100 mg/5 mL) between Weeks 4 and 8, and a second patient (# 1056) received half the prescribed high-dose celecoxib between Week 12 and Week 24. There was 1 patient (# 1169, the same patient as cited above) who received twice the prescribed high-dose celecoxib 12 mg/kg/day (100 mg/5 mL) between Weeks 10 and 16.

The implications of these confounding events, specifically, patients who received increased dosages of the study drug, may have contributed to adverse events.

Table 11. Protocol Inclusion and Exclusion Criterion Violations (JRA and RA)
(Sponsor Table 14, page 67 of 4701)

Center Number*	Subject Number	Treatment Group	Inclusion/Exclusion #	Violation
JRA Subjects				
1018 (69714)	1019	Celecoxib 100 mg/5 mL	JRA Inclusion 4	Subject did not exhibit at least 1 swollen joint and at least 1 joint with limitation of motion at Screening
1018 (69714)	1021	Celecoxib 50 mg/5 mL	JRA Inclusion 4	Subject did not exhibit at least 1 swollen joint and at least 1 joint with limitation of motion at Screening
1018 (69714)	1019	Celecoxib 100 mg/5 mL	JRA Inclusion 6	<10 mm VAS measurement on Physician's and Parent's Global Assessments at Screening
1038 (80998)	1151	Naproxen 125 mg/5 mL	JRA Inclusion 6	<10 mm VAS measurements on Physician's and Parent's Global Assessments at Screening
1085	1355	Naproxen 125 mg/5 mL	JRA Inclusion 12	Parent did not sign ICF prior to study participation
1021 (66525)	1189	Celecoxib 50 mg/5 mL	JRA Exclusion 2	Subject on unstable dose of hydroxychloroquine prior to Screening
1064	1200	Celecoxib 50 mg/5 mL	JRA Exclusion 4	Unstable Plaquenil dose within 12 weeks prior to Screening visit
1023 (68395)	1038	Celecoxib 100 mg/5 mL	JRA Exclusion 4	Exceeded allowable corticosteroid dose
1021 (66525)	1124	Celecoxib 50 mg/5 mL	JRA Exclusion 4	Unstable methotrexate dose within 8 weeks of Screening visit
1021 (66525)	1158	Celecoxib 100 mg/5 mL	JRA Exclusion 4	Unstable methotrexate dose within 8 weeks of Screening visit
1046 (81140)	1177	Naproxen 125 mg/5 mL	JRA Exclusion 4	Subject on unstable dose of etanercept prior to Screening
1021 (66525)	1268	Celecoxib 100 mg/5 mL	JRA Exclusion 4	Exceeded allowable corticosteroid dose
1021 (66525)	1269	Celecoxib 50 mg/5 mL	JRA Exclusion 4	Exceeded allowable corticosteroid dose
1093	1245	Celecoxib 100 mg/5 mL	JRA Exclusion 13	Allergy to sulfonamides
Adult RA Subjects				
1005 (68750)	5015	Celecoxib 200 mg BID	Adult Exclusion 4	Subject was enrolled with positive urine drug screen
1005 (68750)	5013	Celecoxib 200 mg BID	Adult Exclusion 11	Allergy to sulfonamides
1005 (68750)	5040	Celecoxib 200 mg BID	Adult Exclusion 13	Prohibited corticosteroids prior to implementation of Amendment 4
1005 (68750)	5042	Celecoxib 200 mg BID	Adult Exclusion 13	Prohibited corticosteroids prior to implementation of Amendment 4
1005 (68750)	5047	Celecoxib 200 mg BID	Adult Exclusion 13	Corticosteroid dose change within 12 weeks prior to Screening (after approval of Amendment 4)

Abbreviations: VAS = Visual Analog Scale; ICF = Informed Consent Form; JRA = Juvenile Rheumatoid Arthritis; RA = Rheumatoid Arthritis.
* Sites numbers in parentheses are legacy Pharmacia.

Endpoints and Their Statistical Analyses

The primary analysis for the primary efficacy endpoint was the proportion of patients with JRA achieving the JRA DOI 30 criteria [(number of responders (%)] (Celecoxib – Naproxen with 95% CI) at Weeks 2, 4, 8 and 12, with the last observation carried forward (LOCF) in the Intent-To-Treat (ITT) population. Pair-wise treatment comparisons used the Chi-Squared test for the three treatment groups with regard to the proportion of JRA DOI 30 responders at Weeks 2, 4, 8, and 12 (Final visit). Non-inferiority of celecoxib was claimed if the lower limit of the 95% 2-sided confidence interval (CI) for the difference in the percent improved (celecoxib - naproxen) was above -25%.

The secondary analyses included change from Baseline (double-blind Baseline is the last observation prior to the first dose of the double-blind study medication) at each visit (Week 2, 4, 8 and 12) and was analyzed for the core set of 6 variables of the JRA DOI 30. The scale employed ranges from 0-100. Higher scores indicate poorer well-being. A negative change indicates improvement in well-being.

The proportion of JRA patients demonstrating improvement from Baseline, assessed by the Mantel-Haenszel estimate, in the Physician's Global Assessment of Disease Activity (VAS), the Parent's Global Assessment of Overall Well-Being (CHAQ Subsection), Parent's Assessment of Physical Function (CHAQ Disability Index), Parent's Assessment of Child's Arthritis Pain (VAS) [CHAQ subsection], number of joints with active arthritis, number of joints swollen and tender /painful joints assessed separately, number of joints with limited range of motion, CRP, and the Peds QL $^{TM.}$ (Pediatric Quality of Life Inventory, were analyzed as an assessment of health related quality of life.

These analyses were carried out using an analysis of covariance (ANCOVA) model with the treatment group as a factor and the Baseline value as a covariate. The Baseline value, as 1-degree-of-freedom covariate, was used to analyze all continuous efficacy variables based on their time-weighted average response across Weeks 2, 4, 8 and 12. In addition, the assessment of treatment response, celecoxib low dose to celecoxib high dose and each celecoxib treatment group compared to the active comparator, naproxen treatment group, was performed through the least squares (LS) mean changes from Baseline with standard error (SE). The last efficacy assessment was carried forward if a patient withdrew prior to the final visit at 12 Weeks. The sponsor notes that no adjustments were made for multiple comparisons.

The exploratory evaluations included analysis of the percentage of patients with pauciarticular course JRA and, separately, the percentage of patients with polyarticular JRA, who achieved the JRA DOI 30 criterion at Week 12, using the same approach as described above for the primary efficacy endpoint. The same analysis was completed for the percentage of patients who achieved the JRA DOI 50 and JRA DOI 70 for pauciarticular and for polyarticular course JRA.

Persistence of Treatment Effect
Persistence of treatment effect was observed and analyzed from Week 12 to Week 24 for all JRA patients receiving the open-label treatment, high-dose celecoxib. The open-label phase included patients from the following treatment groups in the double-blind phase:

- Low-dose celecoxib treatment group changed to high-dose celecoxib treatment group;
- High-dose celecoxib treatment group remaining the same; and
- Naproxen treatment group changed to high-dose celecoxib treatment group.

Baseline for the open-label phase was the last observation prior to the first dose of open-label study medication; hence, the last observation carried forward approach. Change from the double-blind Baseline to Week 24 (end of the open-label phase) was also calculated. Enrolled patients who took at least one dose of the open-label study medication were included in the analysis. **Applying the JRA DOI 30, the responder rates at the end of the open-label**

extension (Week 24) were 57%, 70% and 71% for low-dose celecoxib, high-dose celecoxib and naproxen, respectively, based on the assigned treatment group from the double-blind phase.

Pharmacokinetic and Pharmacodynamic Analysis
See Clinical Pharmacology review by Srikanth Nallani, PhD., Study RR 754-00049 (RR-049).

Dispositions
Withdrawal due to an adverse event was distinguished from withdrawal due to insufficient response (lack of efficacy) according to the definition of adverse event and/or for other reasons, such as a protocol violation. A flare of systemic features of JRA was added as a criterion for withdrawal of patients from the trial by the sponsor. These events were noted as an adverse event by this medical reviewer. A final evaluation, as required in the protocol, was performed at the time of any study discontinuation.

Discontinuations Due to Lack of Efficacy
The proportion of patients discontinuing study therapy due to lack of efficacy was assessed using the Fisher's exact test. A per protocol analysis, based on predefined exclusion rules, was carried out for the primary endpoint to corroborate the primary efficacy analysis result. The discontinuation rates due to lack of efficacy were 2 (3%), 1 (1%) and 4 (5%) in the celecoxib 3 mg/kg BID treatment group, celecoxib 6 mg/kg BID treatment group and naproxen 7.5 mg/kg BID treatment groups, respectively. See Table 12.

Discontinuations Due to an Adverse Event
The most common reason for early withdrawal from the study was for an adverse event (AE). The discontinuation rates due to an adverse event were 4 (5%), 7 (9%) and 4 (5%) in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively. See Table 12. See Section 7.1 Safety of this review for a detailed discussion of these AEs.

The treatment effect among the patients who completed the 12-week double-blind study was evaluated with the primary endpoint, JRA DOI 30. The analysis was performed among patients who completed the 12-week study, the analysis of the JRA DOI 30 responder, regardless of the completion status. The proportion of patients achieving the JRA DOI 30 in the three treatment groups, and, in the between-treatment comparisons, met the predefined non-inferiority criteria (95% CI for the ratio > 0.25%)

Table 12. Disposition, JRA Patients: Double-Blind and Open-Label Phases, Study 195
(Developed from Sponsor Table 13, page 66 of 4701)

	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day	Total
Randomized to DB Phase	77 (100%)	82 (100%)	83 (100%)	242 (100%)
Completed DB Phase	67 (87%)	71 (87%)	74 (89%)	212 (88%
Early Withdrawal During DB	10 (13%)	11 (15%)	9 (11%)	30 (12%)

	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day	Total
Phase				
Reason for Withdrawn				
Adverse Event	4 (5%)	7 (9%)	4 (5%)	15 (6%)
Protocol violation	0 (0%)	1 (1%)	1 (1%)	2 (1%)
Consent Withdrawn	4 (5%)	2 (2%)	1 (1%)	7 (3%)
Lost to Follow-Up	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Lack of Efficacy	2 (3%)	1 (1%)	4 (5%)	7 (3%)
Completed DB Phase; Did not Enter OL Phase	5 (7%)	1 (1%)	4 (5%)	10 (4%)
Reason for Not Entering OL Phase				
Protocol violation	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Consent Withdrawn	3 (4%)	(1%)1	3 (4%)	7 (3%)
Lack of Efficacy	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Sponsor's Decision	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Enrolled in OL Phase/ Med Taken	62 (100%)	70 (100%)	70 (100%)	202 (100%)
Completed OL Phase	60 (97%)	66 (94%)	69 (99%)	195 (97%)
Early Withdrawal During OL Phase	2 (3%)	4 (6%)	1 (1%)	7 (4%)
Adverse Event	1 (2%)	1* (1%)	1 (1%)	3 (2%)
Protocol Violation	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Consent Withdrawn	0 (0%)	2 (3%)	0 (0%)	2 (1%)
Protocol Specific Withdrawal Criteria	0 (0%)	1 (1%)	0 (0%)	1 (1%)
* Pt # 1044 had sJRA / AEs: sponsored counted as protocol criteria for withdrawal. Abbreviations: DB=double-blind; OL=open-label				

Statistical Analyses Not Performed

The analyses of the JRA DOI 30 core set of variables stratified by drop-out pattern and by the time of drop-out were not carried out because there were too few patients who discontinued due to various reasons to yield meaningful results. This rationale also applies to JRA patients who received more than the proposed total daily dose who were excluded from the non-pre-specified efficacy data set analysis making the number of drop-outs decrease further, hence, there were too few patients to yield meaningful results.

Duration of Exposure

During the double-blind phase of Study 195, there were 77 patients in the low-dose celecoxib treatment group, 82 patients in the high-dose celecoxib treatment group, and 83 patients in the naproxen treatment group who had exposures to study medication of 17, 18 and 19 patient-years, respectively. The majority of patients took their study medication for at least 60 days. See Table

13. According to the sponsor, exposure in patient years to any dose of celecoxib was 80 (38.4%) of patients treated for 168 days.

In the open-label phase, exposure in patient-years to low-dose celecoxib, high-dose celecoxib and to naproxen suspensions was 14, 16, and 16 years, respectively. The sponsor reports that more than 50% of the patients took their open-label study medication for at least 85 days. See Table 14.

Table 13. Duration of Exposure in the Double-Blind Phase, Study 195
(Sponsor Table 17, page 70 of 4701)

	Celecoxib 3 mg/kg BID N (%)		Celecoxib 6 mg/kg BID N (%)		Naproxen 7.5 mg/kg BID N (%)	
Duration in Days						
1-29	8	(10.4%)	6	(7.3%)	2	(2.4%)
30-59	1	(1.3%)	5	(6.1%)	5	(6.0%)
60-93	65	(84.4%)	71	(86.6%)	69	(83.1%)
>93	3	(3.9%)	0	(0.0%)	7	(8.4%)
Number Treated	77		82		83	
Subject-Years of Exposure	17		18		19	

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.
Source: Section 13; Table T19.1

Table 14. Duration of Exposure in the Open-Label Phase by Previous Double-Blind Treatment Group Designation (Sponsor Table 18, page 71 of 4701)

	Celecoxib 3 mg/kg BID N (%)		Celecoxib 6 mg/kg BID N (%)		Naproxen 7.5 mg/kg BID N (%)	
Duration in Days						
1-29	1	(1.6%)	2	(2.9%)	1	(1.4%)
30-59	0	(0.0%)	2	(2.9%)	1	(1.4%)
60-84	30	(48.4%)	29	(41.4%)	25	(35.7%)
85-114	31	(50.0%)	37	(52.9%)	42	(60.0%)
>114	0	(0.0%)	0	(0.0%)	1	(1.4%)
Number Treated	62		70		70	
Subject-Years of Exposure	14		16		16	

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.
Source: Section 13; Table T19.2

EFFICACY RESULTS

Primary Efficacy Endpoint

Based on Celecoxib Suspension, 100 mg to 600 mg, Total Daily Dose

In Study 195, the high-dose of celecoxib, 12 mg/kg/day (100 mg/5 mL), and the low-dose of celecoxib, 6 mg/kg/day (50 mg/5 mL) demonstrated efficacy as measured by the JRA DOI 30 (per cent of responders) and achieved non-inferiority to the active comparator, naproxen

suspension, as noted in the Written Request pre-specified lower limit margin of 0.25 at the 95% confidence interval. See Table 15.

This medical reviewer concurs with the sponsor that at all time points, both celecoxib treatment groups, (inclusive of total daily doses 100 mg to 600 mg) demonstrated non-inferiority to naproxen with numerical treatment differences favoring high-dose celecoxib over naproxen at Weeks 4, 8, and 12, and low-dose celecoxib 6 mg/kg/day at Weeks 2, 4, 8, and 12.

The composite endpoint of response to the JRA DOI 30 criteria did not demonstrate statistical significance between the high-dose celecoxib treatment group and low-dose celecoxib treatment group, though the high-dose celecoxib treatment group trended with a greater numerical outcome by the JRA DOI 30.

Table 15. Primary Efficacy Endpoints: JRA DOI 30 (Intent-To-treat Cohort)
(Sponsor Table 19, page 72 of 4701)

	Celecoxib 3 mg/kg BID N = 77	Celecoxib 6 mg/kg BID N = 82	Naproxen 7.5 mg/kg BID N = 83
Number (%) of Responders[a]	53 (68.83%)	66 (80.49%)	56 (67.47%)
Treatment Comparisons[b]	Difference	95% CI	p-Value
Celecoxib 3 mg/kg BID - Naproxen 7.5 mg/kg BID	+1.36%	(-13.08%, 15.80%)	0.8535
Celecoxib 6 mg/kg BID - Naproxen 7.5 mg/kg BID	+13.02%	(-0.22%, 26.25%)	0.0568

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: CI = Confidence Interval.
[a] A subject was considered a responder by the JRA-30 Definition of Improvement criteria 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 Joint with Active Arthritis; 5) Number of Joints with Limited Range of Motion; 6) Laboratory marker of inflammation (C-Reactive Protein).
[b] Treatment comparisons using Chi-Square test and large sample normal approximation confidence interval.
Source: Section 13; Tables T11.2 and T11.3

Secondary Efficacy Endpoints
Based on Celecoxib Suspension, 100 mg to 600 mg Total Daily Dose

Physician's Global Assessment of Disease Activity (VAS), Double-Blind Phase
The proportion of JRA patients demonstrating improvement from Baseline in the Physician's Global Assessment of Disease Activity (VAS), double-blind phase, demonstrated comparable decreases, (-21.07, -23.27 and -21.88), by the least squares mean change from Baseline to Week 12, across the three treatment groups celecoxib 3 mg/kg BID, celecoxib 6 mg/kg BID and naproxen 7.5 mg/kg BID, respectively. At Week 2, there was statistical significance in the difference between celecoxib 3 mg/kg BID and the active comparator, naproxen, p=0.0138. A statistical difference was not detected between either of the two celecoxib treatment groups, 3mg/kg BID or 6 mg/kg BID versus naproxen 7.5 mg/kg BID at Weeks 4, 8 or 12. See Table 16.

Parent's Global Assessment of Overall Well-Being (CHAQ Subsection, Double-Blind Phase

The decreases in the LS mean change from Baseline to Week 12 were greater for the celecoxib 6 mg/kg BID (-20.85 mm) and naproxen 7.5 mg/kg BID (-20.28) treatment groups than for the celecoxib 3 mg/kg BID (-15.34) treatment group. There were no statistical differences detected between treatment groups using the Parent's Global Assessment of Overall Well-Being (CHAQ subsection). See Table 16.

Parent's Assessment of Physical Function (CHAQ Disability Index)
From Baseline to the Final visit (12-weeks) of the double-blind phase, there was no detectable difference across the three treatment groups, celecoxib 3mg/kf BID, celecoxib 6 mg/kg BID and naproxen 7.5 mg/kg BID, -0.28, -0.32 and -0.31, respectively, using the Parent's Assessment of Physical Function (CHAQ Disability Index). See Table 16.

Number of Joints with Active Arthritis
In the double-blind phase, Baseline to 12 weeks, there was a statistically detectable difference at Week 12 between the two study drug treatments, celecoxib 3 mg/kg BID (-1.94) compared to celecoxib 6 mg/kg BID (-3.54) , LS mean change in the number of joints with active arthritis. The difference between celecoxib 3 mg/kg BID and celecoxib 6 mg/kg BID was 1.60, [95% CI as 0.26, 2.94], p = 0.0199. At Weeks 2, 4, and 8, there was no detectable difference between treatment groups. There was no detectable difference between the celecoxib and naproxen treatment groups. See Table 16.

Number of Joints with Limited Range of Motion
The decreases in the LS mean change from Baseline to Week 12, applying the secondary endpoint, limited range of motion (LOM), demonstrated that there was no detectable difference when comparing either of the celecoxib treatment groups to the naproxen treatment group. When comparing the celecoxib 3 mg/kg BID group to the celecoxib 6 mg/kg BID group, there were two time points with a detectable difference, at Week 8 with a difference of 1.45 [0.42, 2.49], p=0.0062, and at Week 12 was a detectable difference of 1.44 [0.25, 2.63], p=0.0181. See Table 16.

Laboratory Marker of Inflammation (C-Reactive Protein)
In the double-blind phase of Study 195, using the C-Reactive Protein as the marker of inflammation, there was greater decrease in the LS mean change in the low-dose celecoxib treatment group, high-dose celecoxib treatment group and the naproxen treatment group, in descending order, -3.64, -2.67 and -0.01, respectively. There was no detectable difference between either celecoxib treatment group compared to naproxen, or between the low-dose celecoxib versus the high-dose celecoxib treatment group. See Table 16.

Table 16. Secondary Efficacy Endpoints: The 6 Core Set Variables of the JRA DOI 30 at Week 12, Double-Blind Phase.

Secondary Endpoints: 6 Core Set Variables Mean Change Analysis	**Celecoxib 6 mg/kg/day N=77**	**Celecoxib 12 mg/kg/day N-=82**	**Naproxen 15 mg/kg/day N=83**
Physician's Global Assessment of Disease Activity			
Mean Baseline (SD)	42.44 (19.89)	41.05 (17.35)	41.22 (16.25)
Mean Change From Baseline (SD)	-21.58 (20.36)	-22.98 (18.55)	-21.69 (18.74)

Secondary Endpoints: 6 Core Set Variables Mean Change Analysis	Celecoxib 6 mg/kg/day N=77	Celecoxib 12 mg/kg/day N-=82	Naproxen 15 mg/kg/day N=83
Treatment Comparison*		Difference	
Celec 3 mg/kg vs Naproxen		0.81	
Celec 6 mg/kg vs Naproxen		-1.39	
Celec 3 mg/kg vs Celec 6 mg/kg		2.20	
Parent's Global Assessment of Overall Well-Being (CHAQ Subsection)			
Mean Baseline (SD)	38.40 (21.62)	42.65 (19.94)	44.95 (22.67)
Mean Change From Baseline (SD)	-15.34 (27.30)	-20.85 (23.85)	-20.28 (26.94)
Treatment Comparison*		Difference	
Celec 3 mg/kg vs Naproxen		0.29	
Celec 6 mg/kg vs Naproxen		-2.20	
Celec 3 mg/kg vs Celec 6 mg/kg		2.49	
Functional Ability (CHAQ Disability Index)			
Mean Baseline (SD)	0.39 (0.56)	0.35 (0.63)	0.87 (0.67)
Mean Change From Baseline (SD)	-0.29 (0.45)	-0.32 (0.44)	0.31 (0.56)
Treatment Comparison*		Difference	
Celec 3 mg/kg vs Naproxen		0.02	
Celec 6 mg/kg vs Naproxen		-0.02	
Celec 3 mg/kg vs Celec 6 mg/kg		0.04	
Number of Joints with Limited Range of Motion			
Mean Baseline (SD)	8.12 (9.29)	6.68 (8.56)	6.08 (5.99)
Mean Change From Baseline (SD)	-2.40 (5.05)	-3.44 (6.02)	-2.60 (4.74)
Treatment Comparison*		Difference	
Celec 3 mg/kg vs Naproxen		0.99	
Celec 6 mg/kg vs Naproxen		-0.60	
Celec 3 mg/kg vs Celec 6 mg/kg		1.60	
Laboratory Marker of Inflammation (C-Reactive Protein)			
Mean Baseline (SD)	6.60 (8.76)	6.26 (8.25)	4.70 (5.24)
Mean Change From Baseline (SD)	-.35 (4.89)	-2.70 (4.66)	-1.24 (3.36)
Treatment Comparison*		Difference	
Celec 3 mg/kg vs Naproxen		0.42	
Celec 6 mg/kg vs Naproxen		-1.02	
Celec 3 mg/kg vs Celec 6 mg/kg		1.44	
All celecoxib and naproxen doses were administered BID; Celec=Celecoxib;			

Open-Label Phase

Physician Global Assessment of Disease Activity (VAS)

The treatment effect persisted from Weeks 12 to 24 for all patients receiving low-dose celecoxib, high-dose celecoxib and naproxen was 0.60 mm, -1.40 mm, and -4.87 mm, respectively. The overall mean change using the Physician Global Assessment of Disease Activity (VAS), open-label phase was -1.99 mm. There were no detectable statistical differences between treatment groups using the Physician Global Assessment of Disease Activity (VAS). See Table 17.

Table 17. Physician Global Assessment of Disease Activity (VAS) in the Open-Label Phase: Intent-To-Treat Cohort, LOCF (Information from Sponsor Table T5.5, page 137 of 4701)

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Overall N=202
Baseline				
N	62	70		
Mean (SD)	41.85 (18.16)	41.35 (17.88)		
Week 12				
N	62	70	70	202
Mean (SD)	17.60 (13.65)	15.86 (14.39)	14.99 (12.99)	16.09 (13.66)
Week 24				
N	62	70	70	202
Mean (SD)	18.19 (20.37)	14.46 (16.86)	10.11 (10.44)	14.10 (16.48)
Change from Baseline to Wk 24				
N	62	70		
Mean Change (SD)	-23.66 (20.38)	-26.89 (19.36)		
Change from Wk 12 to Wk 24				
N	62	70	70	202
Mean Change (SD)	0.60 (15.55)	-1.40 (11.83)	-4.87 (11.59)	-1.99 (13.14)

Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. This scale ranges from 0-100. Higher scores indicate poorer well-being. The data in this table is based on the last observation carried forward (LOCF) approach.

Open-Label Phase

Parent's Global Assessment of Overall Well-being (VAS) [CHAQ subsection]

As measured by the Parent's Global Assessment of Overall Well-being (VAS) (CHAQ subsection), the treatment effect persisted from Weeks 12 to 24 for all patients receiving the open-label treatment with low-dose celecoxib, high-dose celecoxib and naproxen as a mean change of 1.27 mm, -1.08 mm and -6.61 mm, respectively. The overall open-label phase mean change was -2.27mm across the three treatment groups based on the previous treatment assignment. See Table 18.

Table 18. Parent's Global Assessment of Overall Well-Being (VAS) CHAQ Subsection) Open-Label Phase: Intent-To-Treat Cohort, LOCF
(Information from Sponsor Table T6.5, page 142 of 4701)

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	**Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Overall N=202**
Baseline				
N	62	70		
Mean (SD)	39.10 (21.10)	42.61 (20.30)		
Week 12				
N	62	70	70	202
Mean (SD)	18.40 (16.36)	17.98 (16.99)	21.13 (20.15)	19.20 (17.94)
Week 24				
N	62	70	70	202
Mean (SD)	19.68 (23.10)	16.90 (20.12)	14.51 (15.31)	16.93 (19.64)
Change from Baseline to Wk 24				
N	62	70		
Mean Change (SD)	-19.42 (26.30)	-25.71 (26.84)		
Change from Wk 12 to Wk 24				
N	62	70	70	202
Mean Change (SD)	1.27 (23.17)	-1.08 (19.40)	-6.61 (18.88)	-2.27 (20.62)
Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. This scale ranges from 0-100. Higher scores indicate poorer well-being. The data in this table is based on the last observation carried forward (LOCF) approach.				

Open-Label Phase

Functional Ability (CHAQ: Disability Index)

In the Open-Label Extension Phase from Weeks 12 to 24, a treatment effect for functional ability (CHAQ: Disability Index) was observed as -0.50, 0.01, and -0.06 in the treatment groups low-dose celecoxib changed to high-dose celecoxib, high-dose celecoxib continued on high-dose celecoxib and naproxen changed to high-dose celecoxib, respectively. The overall treatment effect in the open-label phase for functional ability was -0.03. There was no detectable difference among the three treatment groups based on the previous double-blind treatment assignment. See Table 19.

Table 19. Functional Ability (CHAQ: Disability Index) in the Open-Label Phase, LOCF
(Portion of data from Sponsor Table T7.5, page 147 of 4701)

	Celecoxib 6 mg/kg/day, 50 mg/5 mL to Celecoxib 12 mg/kg/day 100mg/5mL N= 62	Celecoxib 12 mg/kg/day 100 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Naproxen 15 mg/kg/day 125 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Overall N=202
Baseline				
N	62	70		
Mean (SD)	0.85 (0.56)	0.84 (0.60)		
Week 12				

N Mean (SD)	62 0.52 (0.53)	70 0.51 (0.57)	70 0.48 (0.48)	202 0.50 (0.52)
Week 24 N Mean (SD)	 62 0.47 (0.53)	 70 0.52 (0.56)	 70 0.42 (0.47)	 202 0.47 (0.52)
Change from Baseline to Wk 24 N Mean Change (SD)	 62 -038 (0.42)	 70 -0.32 (0.48)		
Change from Wk 12 to Wk 24 N Mean Change (SD)	 62 -0.05 (0.33)	 70 0.01 (0.29)	 70 -0.06 (0.24)	 202 -0.03 (0.29)
Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. This scale ranges from 0-3. Higher scores indicate poorer physical functioning. The data in this table is based on the last observation carried forward (LOCF) approach.				

Open-Label Phase

Number of Joints with Active Arthritis

In the open-label phase (Weeks 12 to 24) analyzed by the number of joints with active arthritis, there was no detectable difference among the three treatment groups. A treatment effect for the number of joints with active arthritis was observed as the mean change of - 0.19, - 0.07 and - 0.60 in the treatment groups low-dose celecoxib changed to high-dose celecoxib, high-dose celecoxib maintained as the same dose, and naproxen changed to high-dose celecoxib, respectively. The overall treatment effect in the open-label phase for the number of joints with active arthritis was - 0.29. See Table 20.

Table 20**.** Number of Joints with Active Arthritis in the Open-Label Phase, ITT, LOCF
(Portion of data from Sponsor Table T8.5, page 152 of 4701)

	Celecoxib 6 mg/kg/day, 50 mg/5 mL to Celecoxib 12 mg/kg/day 100mg/5mL N= 62	Celecoxib 12 mg/kg/day 100 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Naproxen 15 mg/kg/day 125 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Overall N=202
Baseline N Mean (SD)	 62 7.94 (9.32)	 70 7.16 (9.13)		
Week 12 N Mean (SD)	 62 4.68 (8.18)	 70 3.21 (4.43)	 70 2.77 (4.80)	 202 3.51 (5.96)
Week 24 N Mean (SD)	 62 4.48 (8.62)	 70 3.14 (5.59)	 70 2.17 (3.89)	 202 3.22 (6.27)
Change from Baseline to Wk 24 N Mean Change (SD)	 62 -3.45 (6.98)	 70 -4.01 (8.49)		
Change from Wk 12 to				

Wk 24				
N	62	70	70	202
Mean Change (SD)	-0.19 (3.40)	-0.07 (4.25)	-0.60 (3.53)	- 0.29 (3.75)
Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. A joint is considered active if it is swollen (not due to currently inactive synovitis or to bony enlargement from previously active disease). If no swelling is present, the joint is considered active if it has limited range of motion accompanied by pain or tenderness. Pain and/or tenderness alone are not sufficient for classification of the joint as being active. The data in this table is based on the last observation carried forward (LOCF) approach.				

Open-Label Phase

Number of Joints with Limited Range of Motion

In the open-label phase (Weeks 12 to 24) analyzed by the number of joints with limited range of motion, there was no detectable difference among the three treatment groups. A treatment effect for the number of joints with limited range of motion was observed, by the mean change of 0.21, 0.07, and -0.50, in the treatment groups, low-dose celecoxib changed to high-dose celecoxib, high-dose celecoxib maintained as the same dose and naproxen changed to high-dose celecoxib, respectively. The overall treatment effect in the open-label phase for the number of joints with limited range of motion was -0.08, based on the previous double-blind treatment assignment. See Table 21.

Table 21. Number of Joints with Limited Range of Motion in the Open-Label Phase: Intent-To-Treat Cohort, LOCF (Portion of data from sponsor Table T9.5, page 157 of 4701)

	Celecoxib 6 mg/kg/day 50 mg/5 mL to Celecoxib 12 mg/kg/day 100mg/5mL N= 62	Celecoxib 12 mg/kg/day 100 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Naproxen 15 mg/kg/day 125 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Overall N=202
Baseline				
N	62	70		
Mean SD	6.18 (8.69)	6.51 (8.79)		
Week 12				
N	62	70	70	202
Mean SD	4.71 (8.27)	3.89 (6.30)	2.87 (5.25)	3.79 (6.67)
Week 24				
N	62	70	70	202
Mean SD	4.92 (9.13)	3.96 (6.52)	2.37 (4.79)	3.70 (6.98)
Change from Baseline to Wk 24				
N	62	70		
Mean Change (SD)	-1.27 (5.74)	-2.86 (5.83)		
Change from Wk 12 to Wk 24				
N	62	70	70	202
Mean Change (SD)	0.21 (4.08)	0.07 (3.41)	-0.50 (2.62)	-0.08 (3.39)
Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study				

medication. The data in this table is based on the last observation carried forward (LOCF) approach.

Open-Label Phase

Laboratory Marker of Inflammation

In the open-label extension phase, (Week 12 to Week 24), a treatment effect was observed in each of the treatment groups; however, there was no detectable difference in the mean changes. The largest mean change in the open-label extension from Baseline to Week 24 was in the high-dose celecoxib treatment group, -4.30, compared to low-dose celecoxib treatment group with -1.61. See Table 22

Table 22. Laboratory Marker of Inflammation (C-Reactive Protein) in the Open-Label Phase: Intent-To-Treat Cohort, LOCF (Portion of data from sponsor Table T10.5, page 162 of 4701)

	Celecoxib 6 mg/kg/day 50 mg/5 mL to Celecoxib 12 mg/kg/day 100mg/5mL N= 62	Celecoxib 12 mg/kg/day 100 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Naproxen 15 mg/kg/day 125 mg/5 mL to Celecoxib 12 mg/kg/day 100 mg/5 mL N=70	Overall N=202
Baseline				
N	62	70		
Mean (SD)	13.15 (30.87)	16.54 (33.41)		
Week 12				
N	62	70	70	202
Mean (SD)	10.50 (18.05)	12.52 (27.65)	10.68 (16.12)	11.26 (24.42)
Week 24				
N	62	70	70	202
Mean (SD)	11.64 (16.58)	12.29 (23.53)	8.51 (18.14)	10.78 (19.73)
Change from Baseline to Wk 24				
N	62	70		
Mean Change (SD)	-1.61 (29.54)	-4.30 (23.91)		
Change from Wk 12 to Wk 24				
N	62	70	70	202
Mean Change (SD)	1.14 (18.19)	-0.23 (21.26)	-2.17 (16.86)	-0.48 (18.84)

Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. The data in this table is based on the last observation carried forward (LOCF) approach.

OTHER EVALUATIONS

Celecoxib Suspension 100 mg to 600 mg Total Daily Dose

Parent's Assessment of Child's Arthritis Pain (CHAQ Subsection), Double-Blind Phase

The LS mean change across the three treatment groups was comparable as -19.28, -21.43 and -19.11 for low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively.

There was no detectable difference among the three treatment groups nor was there a detectable difference comparing the two celecoxib treatment groups. See Table 23.

Table 23. Parent's Assessment of Child's Arthritis Pain (VAS) (CHAQ Subsection) in the Double-blind Phase, Baseline to Week 12: Intent-To-Treat Population
(Sponsor Table 26, page 87 of 4701)

Mean Change Analysis	Celecoxib 3 mg/kg BID (N = 77)		Celecoxib 6 mg/kg BID (N = 82)		Naproxen 7.5 mg/kg BID (N = 83)	
Week 2						
Mean Baseline (SD)	41.31	(24.46)	41.45	(21.40)	42.66	(20.81)
Mean Change From Baseline (SD)	-10.98	(21.24)	-11.77	(21.29)	-11.35	(21.52)
LS Mean Change From Baseline (SE)[b]	-11.20	(2.17)	-11.93	(2.10)	-10.98	(2.10)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.22		[-6.17, 5.72]	0.9418		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.95		[-6.80, 4.90]	0.7494		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	0.73		[-5.21, 6.67]	0.8093		
Week 4						
Mean Baseline (SD)	41.31	(24.46)	41.45	(21.40)	42.66	(20.81)
Mean Change From Baseline (SD)	-15.90	(23.77)	-16.29	(21.81)	-17.07	(24.67)
LS Mean Change From Baseline (SE)[b]	-16.19	(2.25)	-16.50	(2.18)	-16.59	(2.18)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	0.40		[-5.77, 6.58]	0.8982		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	0.09		[-5.99, 6.16]	0.9774		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	0.31		[-5.86, 6.49]	0.9203		
Week 8						
Mean Baseline (SD)	41.31	(24.46)	41.45	(21.40)	42.66	(20.81)
Mean Change From Baseline (SD)	-16.39	(23.71)	-17.64	(24.60)	-16.49	(25.95)
LS Mean Change From Baseline (SE)[b]	-16.65	(2.51)	-17.83	(2.43)	-16.05	(2.43)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.60		[-7.49, 6.30]	0.8650		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-1.78		[-8.56, 5.00]	0.6061		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	1.18		[-5.71, 8.07]	0.7357		
Week 12						
Mean Baseline (SD)	41.31	(24.46)	41.45	(21.40)	42.66	(20.81)
Mean Change From Baseline (SD)	-18.94	(23.54)	-21.18	(26.37)	-19.68	(28.59)
LS Mean Change From Baseline (SE)[b]	-19.28	(2.46)	-21.43	(2.39)	-19.11	(2.39)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.17		[-6.93, 6.58]	0.9603		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-2.32		[-8.97, 4.33]	0.4920		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	2.15		[-4.60, 8.90]	0.5309		

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: LS = Least Squares; SD = Standard Deviation; SE = Standard Error; CI = Confidence Interval.
[a] Double-blind Baseline is the last observation prior to the first dose of double-blind study medication. This scale ranges from 0-100. Higher scores indicate worse pain. A negative mean change indicates improvement.
[b] From ANCOVA model with treatment group as a factor and Baseline value as covariate.
[c] From a contrast statement from ANCOVA model in footnote b.
Source: Section 13; Tables T14.2 and T14.3.

Open-Label Phase

Parent's Assessment of Child's Arthritis Pain (VAS)

In the open-label extension phase, using the Parent's Assessment of Child's Arthritis Pain (VAS) (CHAQ Subsection), there was no detectable difference by Week 24 from Baseline, high-dose celecoxib treatment group mean change was -24.24 and low-dose celecoxib treatment group mean change was -21.27. The scale ranges from 0 to 100. Higher scores indicate worse pain. A treatment effect was observed from Week 12 to Week 24 in each treatment group, high-dose

celecoxib 12 mg/kg/day, low-dose celecoxib 6 mg/kg/day, and naproxen 15 mg/kg/day treatment groups, -0.19, 0.16 and -6.14, respectively. See Table 24.

Table 24. Parent's Assessment of Child's Arthritis Pain (VAS) (CHAQ Subsection) in the Open-Label Phase, Last Observation Carried Forward (LOCF)
(Portion of data from sponsor Table 14.5, page 190 of 4701)

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Overall N=202
Baseline				
N	62	70		
Mean (SD)	40.19 (23.27)	40.34 (20.80)		
Week 12				
N	62	70	70	202
Mean (SD)	18.76 (18.08)	16.79 (16.95)	19.69 (20.78)	18.40 (18.64)
Week 24				
N	62	70	70	202
Mean (SD)	18.92 (24.63)	16.60 (19.81)	13.56 (15.22)	16.26 (20.08)
Change from Baseline to Wk 24				
N	62	70		
Mean Change (SD)	-21.27 (23.99)	-24.24 (14.02)		
Change from Wk 12 to Wk 24				
N	62	70	70	202
Mean Change (SD)	0.16 (24.04)	-0.19 (15.49)	-6.14 (18.98)	-2.14 (19.75)

Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. The scale ranges from 0 to 100. Higher scores indicate worse pain. The data in this table is based on the last observation carried forward (LOCF) approach.

Peds QL ™; Pediatric Quality of Life Inventory, Double-Blind Phase

The Pediatric Quality of Life was completed at Baseline and at Week 12 to assess health related quality of life for patients with JRA. There were two reports, the Child's Self-Report and the Parent Report, analyzed by the LS mean change for patients in the double-blind phase. There was no detectable between-treatment group differences observed in any of the PedsQL TM scores using either the Child or the Parent instrument. See Table 25 and 26.

Table 25. Pediatric Quality of Life Inventory, Total Score: Child Self-Report in the Double-Blind Phase, Baseline to Week 12: Intent-To-Treat Population
(Sponsor Table 27, page 89 of 4701)

Mean Change Analysis at Week 12	Celecoxib 3 mg/kg BID (N = 77)		Celecoxib 6 mg/kg BID (N = 82)		Naproxen 7.5 mg/kg BID (N = 83)	
Physical Health Summary Score						
Mean Baseline (SD)	60.43	(21.38)	61.22	(19.71)	61.34	(19.70)
Mean Change From Baseline (SD)	7.31	(18.63)	9.03	(16.91)	8.81	(14.56)
LS Mean Change From Baseline (SE)[b]	7.12	(1.96)	9.10	(1.93)	8.92	(1.86)
Treatment Comparisons[c]	Difference		95% CI	P-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-1.79		[-7.12, 3.53]	0.5067		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	0.18		[-5.09, 5.46]	0.9456		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-1.98		[-7.40, 3.44]	0.4726		
Psychosocial Health Summary Score						
Mean Baseline (SD)	70.20	(17.86)	70.68	(14.37)	69.26	(17.08)
Mean Change From Baseline (SD)	2.60	(14.89)	5.29	(11.57)	6.82	(13.15)
LS Mean Change From Baseline (SE)[b]	2.66	(1.52)	5.52	(1.50)	6.55	(1.45)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-3.90		[-8.04, 0.25]	0.0650		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-1.04		[-5.15, 3.07]	0.6191		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-2.86		[-7.08, 1.36]	0.1827		
Total Scale Score						
Mean Baseline (SD)	66.80	(17.00)	67.40	(14.90)	66.51	(15.89)
Mean Change From Baseline (SD)	4.22	(13.88)	6.60	(11.73)	7.51	(11.92)
LS Mean Change From Baseline (SE)[b]	4.20	(1.47)	6.75	(1.45)	7.39	(1.40)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-3.2		[-7.2, 0.8]	0.1170		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.6		[-4.6, 3.3]	0.7495		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-2.6		[-6.6, 1.5]	0.2184		

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: LS = Least Squares; SD = Standard Deviation; SE = Standard Error; CI = Confidence Interval.
[a] Double-blind Baseline is the last observation prior to the first dose of double-blind study medication. This scale ranges from 0-100. Higher scores indicate better well-being. A positive mean change indicates improvement.
[b] From ANCOVA model with treatment group as a factor and Baseline value as covariate.
[c] From a contrast statement from ANCOVA model in footnote b.
Source: Section 13; Tables T15.2, T15.3, T16.2, T16.3, T17.2, and T17.3.

Table 26. Pediatric Quality of Life Inventory, Total Score: Parent Report from the Double Blind Phase, Baseline to Week 12: Intent-To-Treat Population (Sponsor Table 28, page 90 of 4701)

Mean Change Analysis at Week 12	Celecoxib 3 mg/kg BID (N = 77)		Celecoxib 6 mg/kg BID (N = 82)		Naproxen 7.5 mg/kg BID (N = 83)	
Physical Health Summary Score						
Mean Baseline (SD)	56.31	(19.96)	59.84	(21.32)	58.29	(21.48)
Mean Change From Baseline (SD)	10.05	(18.44)	10.75	(19.82)	10.65	(18.61)
LS Mean Change From Baseline (SE)[b]	9.32	(1.97)	11.39	(1.91)	10.69	(1.91)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-1.37		[-6.78, 4.04]	0.6188		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	0.70		[-4.62, 6.02]	0.7958		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-2.07		[-7.48, 3.35]	0.4529		
Psychosocial Health Summary Score						
Mean Baseline (SD)	68.10	(18.14)	71.51	(16.00)	69.36	(18.05)
Mean Change From Baseline (SD)	5.81	(14.07)	4.78	(13.37)	6.16	(12.80)
LS Mean Change From Baseline (SE)[b]	5.30	(1.40)	5.37	(1.36)	6.06	(1.35)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.76		[-4.60, 3.08]	0.6967		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.69		[-4.47, 3.09]	0.7191		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-0.07		[-3.92, 3.78]	0.9717		
Total Scale Score						
Mean Baseline (SD)	63.79	(17.06)	67.36	(15.95)	65.38	(17.82)
Mean Change From Baseline (SD)	7.34	(13.11)	6.90	(13.81)	7.72	(13.08)
LS Mean Change From Baseline (SE)[b]	6.80	(1.41)	7.45	(1.37)	7.67	(1.37)
Treatment Comparisons[c]	Difference		95% CI	p-Value		
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.9		[-4.7, 3.0]	0.6565		
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg BID	-0.2		[-4.0, 3.6]	0.9103		
Celecoxib 3 mg/kg BID vs Celecoxib 6 mg/kg BID	-0.7		[-4.5, 3.2]	0.7392		

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: LS = Least Squares; SD = Standard Deviation; SE = Standard Error; CI = Confidence Interval.
[a] Double-blind Baseline is the last observation prior to the first dose of double-blind study medication. This scale ranges from 0-100. Higher scores indicate better well-being. A positive mean change indicates improvement.
[b] From ANCOVA model with treatment group as a factor and Baseline value as covariate.
[c] From a contrast statement from ANCOVA model in footnote b.
Source: Section 13; Tables T15.5, T15.7, T16.5, T16.7, T17.5, and T17.7.

Open-Label Phase

Pediatric Quality of Life Inventory, Physical Health Summary of the Child's Self Report

In the open-label phase, using the Pediatric Quality of Life Inventory, Physical Health Summary of the Child's Self-Report, the low-dose celecoxib, appears to demonstrate better treatment effect, as measured by the mean change from Baseline to Week 24, 12.13 (SD 20.74). High-dose celecoxib demonstrates a mean change of 11.24 (18.89). See Table 27. There is no detectable difference between the two celecoxib treatment groups or among the three treatment groups, including the active comparator, naproxen.

Open-Label Phase

Pediatric Quality of Life Inventory, Physical Health Summary of the Parent's Report,

In the open-label phase, using the Pediatric Quality of Life Inventory, Physical Health Summary of the Parent's Report, the mean change from Baseline to Week 24 is almost the same in the two celecoxib treatment groups, low-dose celecoxib (15.70 mean change) compared to high-dose celecoxib, (15.71 mean change). Naproxen, the active comparator, trended more than either

celecoxib study treatment group with the mean change from Baseline to Week 12 (71.74 mean change), and Week 24 (79.32 mean change). There was no detectable difference between the two celecoxib treatment groups, in the mean change from Week 12 to Week 24, celecoxib 6 mg/kg/day (mean change, 3.78) compared to celecoxib 12 mg/kg/day group (mean change, 3.68). See Table 28.

Table 27. Pediatric Quality of Life Inventory, Physical Health Summary, Child's Self-Report in the Open-Label Phase: Intent-To-Treat Population, LOCF
(Data from portion of sponsor Table T15.4, page 194 of 4701)

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	**Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Overall N=202**
Baseline				
N	50	55		
Mean (SD)	61.94 (20.10)	62.45 (19.340		
Week 12				
N	52	56	60	169
Mean (SD)	71.15 (21.01)	72.89 (18.97)	73.22 (16.88)	72.47 (18.83)
Week 24				
N	53	58	62	173
Mean (SD)	73.41 (20.77)	74.57 (20.30)	78.43 (16.45)	75.60 (15.17)
Change from Baseline to Wk 24				
N	50	55		
Mean Change (SD)	12.13 (20.74)	11.24 (18.89)		
Change from Wk 12 to Wk 24				
N	52	56	60	168
Mean Change (SD)	2.22 (18.36)	1.22 (10.24)	4.90 (17.01)	2.85 (15.56)

Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. The scale ranges from 0 to 100. Higher scores indicate better well-being. The data in this table is based on the last observation carried forward (LOCF) approach.

Table 28. Pediatric Quality of Life Inventory, Physical Health Summary, Parent Report in the Open-Label Phase: Intent-To-Treat Population, LOCF
(Data in this table from sponsor Table 15.8, page 198 of 4701))

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	**Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70**	**Overall N=202**
Baseline				
N	61	70		
Mean (SD)	56.79 (19.87)	60.89 (21.75)		
Week 12				
N	62	70	69	201

	Celecoxib 6 mg/kg/day to Celecoxib 12 mg/kg/day N= 62	Celecoxib 12 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Naproxen 15 mg/kg/day to Celecoxib 12 mg/kg/day N=70	Overall N=202
Mean (SD)	68.80 (21.55)	72.93 (19.80)	71.74 (18.56)	71.25 (19.92)
Week 24				
N	62	70	70	202
Mean (SD)	72.58 (24.27)	76.61 (19.06)	79.32 (17.13)	76.31 (20.29)
Change from Baseline to Wk 24				
N	61	70		
Mean Change (SD)	15.70 (21.47)	15.71 (19.93)		
Change from Wk 12 to Wk 24				
N	62	70	69	201
Mean Change (SD)	3.78 (19.08)	3.68 (14.19)	7.51 (17.09)	5.02 (16.82)

Baseline for the double-blind phase is the last observation prior to the first dose of double-blind study medication, and Baseline for the open-label phase is the last observation prior to the first dose of the open-label study medication. The scale ranges from 0 to 100. Higher scores indicate better well-being. The data in this table is based on the last observation carried forward (LOCF) approach.

EXPLORATORY ANALYSES
Based on Celecoxib Suspension, 100 mg to 600 mg Total Daily Dose

JRA DOI 30, Pauciarticular and Polyarticular course JRA, Double-Blind

This medical reviewer concurs with the sponsor's results, the percentage of patients with polyarticular course JRA who met the JRA DOI 30 criterion at Week 12 was 63% for the low-dose celecoxib, 84% for high-dose celecoxib and 57% for the naproxen group. At Week 12, both of the low-dose and the high-dose celecoxib treatment groups demonstrated non-inferiority to naproxen.

The percentage of patients with **pauciarticular JRA** who achieved the **JRA DOI 30** criterion at Week 12 (double-blind phase) was **76%, 78% and 79%** for **low-dose celecoxib, high-dose celecoxib** and **naproxen** treatment groups, respectively.

In the analysis of JRA, by polyarticular or pauciarticular course, there was a **detectable difference with the JRA DOI 30 response rate** ($p = 0.0110$) for **polyarticular course JRA** treated with **high-dose celecoxib** at Week 12 compared to the naproxen treatment group.

JRA-50 Definition of Improvement

The response rates for the **JRA DOI 50** for the **low-dose celecoxib, high-dose celecoxib and the naproxen group were 56%, 61% and 55%, respectively.** There was not a detectable difference among the three treatment groups at Week 8 and Week 12. The high-dose celecoxib treatment group trended better than did the naproxen treatment group. See Table 29.

Table 29. JRA-50 Definition of Improvement at Week 12, Double-Blind Phase
(Sponsor Table 29, page 91 of 4701)

	Celecoxib 3 mg/kg BID (N = 77)	Celecoxib 6 mg/kg BID (N = 82)	Naproxen 7.5 mg/kg BID (N = 83)
JRA-50 Definition of Improvement			
Number (%) of Responders[a]	43 (55.84%)	50 (60.98%)	46 (55.42%)
Treatment Comparisons[b]	(Celecoxib - Naproxen)		
Difference % Responders	+0.42%	+5.56%	
95% Confidence Interval	[-14.98%, 15.83%]	[-9.47%, 20.58%]	
p-Value	0.9571	0.4696	

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.

[a] A subject was considered a responder by the JRA-50 Definition of Improvement criteria if there is a ≥50% improvement in ≥3 JRA Core Set variables and a >30% worsening in at most 1 JRA Core Set variable.

[b] Treatment comparisons using Chi-Squared test.

Source: Section 13; Tables T11.5 and T11.6

JRA-70 Definition of Improvement

The exploratory analysis, using the **JRA DOI 70**, at Week 12 demonstrated **25%, 37%, 33%** for the **low-dose celecoxib, high-dose celecoxib** and the **naproxen treatment groups.** Both celecoxib treatment groups demonstrated non-inferiority to naproxen. See Table 30.

Table 30. JRA – 70 Definition of Improvement, Week 12, Double-Blind Phase
(Sponsor Table 30, page 92 of 4701)

	Celecoxib 3 mg/kg BID (N = 77)	Celecoxib 6 mg/kg BID (N = 82)	Naproxen 7.5 mg/kg BID (N = 83)
JRA-70 Definition of Improvement			
Number (%) of Responders[a]	19 (24.68%)	30 (36.59%)	27 (32.53%)
Treatment Comparisons[b]	(Celecoxib - Naproxen)		
Difference % Responders	-7.85%	+4.06%	
95% Confidence Interval	[-21.79%, 6.08%]	[-10.45%, 18.56%]	
p-Value	0.2727	0.5839	

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.

[a] A subject was considered a responder by the JRA-70 Definition of Improvement criteria if there is a ≥70% improvement in ≥3 JRA Core Set variables and a >30% worsening in at most 1 JRA Core Set variable.

[b] Treatment comparisons using Chi-Squared test.

Source: Section 13; Tables T11.8 and T11.9

JRA-DOI 30 at WEEK 24 [NON PRE-SPECIFIED ANALYSIS]

As the open-label phase only included high-dose celecoxib, efficacy analyses were not performed.

ADDITIONAL EFFICACY ANALYSES [NON PRE-SPECIFIED ANALYSES]

Celecoxib Suspension, 100 mg to 200 mg Total Daily Dose, PROPOSED DOSAGE

(Note: Section 8.5 Advisory Committee Meeting for comments about sub-group analyses presented by the sponsor to demonstrate efficacy with the proposed celecoxib doses compared to the studied celecoxib doses.)

Primary Efficacy Endpoint, JRA DOI 30

The sponsor proposes a daily dose of celecoxib 50 mg BID (100 mg total daily dose) for JRA patients with body weight ≥ 10 kg to ≤ 25 kg, and a daily dose of celecoxib 100 mg BID (200 mg total daily dose) for JRA patients with body weight > 25 kg. In Study 195, patients were treated with celecoxib suspension total daily doses greater than or equal to 100 mg up to 600 mg per day. See Table 31.

Table 31. Dosage Based on Volume: Patients with JRA
(Sponsor Table 5, page 43 of 4701)

Weight	Celecoxib Low-Dose Suspension (3 mg/kg BID)	Celecoxib High-Dose Suspension (6 mg/kg BID)	Naproxen Suspension (7.5 mg/kg BID)
9-12 kg	25 mg BID (50 mg TDD)	50 mg BID (100 mg TDD)	62.5 mg BID (125 mg TDD)
13-25 kg	50 mg BID (100 mg TDD)	100 mg BID (200 mg TDD)	125 mg BID (250 mg TDD)
26-37 kg	75 mg BID (150 mg TDD)	150 mg BID (300 mg TDD)	187.5 mg BID (375 mg TDD)
38-50 kg	100 mg BID (200 mg TDD)	200 mg BID (400 mg TDD)	250 mg BID (500 mg TDD)
>50 kg	150 mg BID (300 mg TDD)	300 mg BID (600 mg TDD)	500 mg BID (1000 mg TDD)

Note: Celecoxib Low-Dose Suspension = 50 mg/5 mL; Celecoxib High-Dose Suspension = 100 mg/5 mL; Naproxen Suspension = 125 mg/5 mL.
Abbreviations: BID = Twice Daily; TDD = Total Daily Dose; mg = Milligram; kg = Kilogram; mL = Milliliter.

Sixty-five of the 242 randomized patients received celecoxib suspension in total daily doses greater than the proposed dosage, 100 or 200 mg per day, based on total body weight. Therefore, 177 patients remained in Study 195, across the two treatment groups, who actually received study medication within the proposed celecoxib dosage range. See Table 32.

Table 32. Celecoxib Suspension, Total Daily Dose without the 600, 400 and 300 mg Cohorts, by Treatment Group, Double-Blind Phase of Study 195

Celecoxib Suspension TDD	Total Patients N = 242	Celecoxib 6 mg/kg/day N= 77	Celecoxib, 12 mg/kg/day N = 82	Naproxen 15 mg/kg/day N = 83
W/O 600 mg TDD Cohort	225	NA	17*	NA
W/O 600 and 400 mg TDD Cohorts	211	NA	14*	NA
W/O 600, 400, 300 mg TDD Cohorts	177	18*	16*	NA
Balance of patients remaining in Study 195	**177**	**59**	**35**	NA
Abbreviations: TDD = Total Daily Dose; mg = milligrams; kg = kilogram; N = total number of patients; NA = Not Applicable; W/O = without; * denotes different patients.				

Table 33 presents the patient data, stratified by Baseline weight, for JRA patients who were treated with the proposed celecoxib doses, 50 mg BID (100 mg TDD) for patients ≥ 10 kg to ≤ 25 kg, and celecoxib 100 mg BID (200 mg TDD) for JRA patients with total body weight > 25 kg.
Among the 177 remaining patients, there were 58 patients in the celecoxib 6 mg/kg/day treatment group, 30 patients in the celecoxib 12 mg/kg/day treatment group and 83 patients in the naproxen 15 mg/kg/day treatment group. There are **0 patients in the low-dose celecoxib treatment group (100 mg TDD) and 2 patients in the high-dose celecoxib treatment group (200 mg TDD) with weight ≥ 9 kg to < 12 kg.**

There are 21 patients in the low-dose celecoxib treatment group (100 mg TDD) and 28 patients in the high-dose celecoxib treatment group (200 mg TDD) > 12 kg to ≤ 25 kg. There are 37 patients > 25 kg in the low-dose celecoxib treatment group (200 mg TDD or less) and 0 patients > 25 kg in the high-dose celecoxib treatment group (200 mg TDD or less). See Table 33 and 34.

There were only 3 children with body weight between 12 kg and 13 kg who were treated with low-dose celecoxib suspension. There were only 4 children with **body weight between 13 kg and 14 kg,** 2 of these children were treated with naproxen and **only 2 were treated with high-dose celecoxib.**

Table 33. Celecoxib Suspension, Based on Baseline Weight, **Administered 100 mg or 200 mg TDD),** Double-Blind Phase (Weight at Baseline)

Weight	Celecoxib 6 mg/kg/day, 50 mg/5 mL	Celecoxib 12 mg/kg/day, 100 mg/5mL	Naproxen 15 mg/kg/day, 125 mg/5mL
Total patients who received 100 to 200 mg TDD	**58**	**30**	**85**
≥ 9 kg to ≤ 12 kg	0	2	0
> 12 kg to ≤ 25 kg	21	28	22
> 25 kg to ≤ 37 kg	20	0	20
> 37 kg to ≤ 50 kg	17	0	22
> 50 kg	0	0	21
Abbreviations: kg=kilograms			

Table 34. Celecoxib Suspension, Based on Baseline Weight, Administered 100 mg or 200 mg TDD in the Double-Blind Phase. **Non Pre-specified Sub-Analysis of JRA DOI 30**

	Celecoxib 6 mg/kg/day, 50 mg/5 mL	Celecoxib 12 mg/kg/day, 100 mg/5mL	Naproxen 15 mg/kg/day, 125 mg/5mL
Total Patients	**58**	**30**	**85**
Weight Category			
≥ 9 kg to ≤ 12 kg	N = 0 25 mg BID (50 mg TDD)	N =2 50 mg BID (100 mg TDD)	N = 0 62.5 mg BID 125 mg TDD)
> 12 kg to ≤ 25 kg	N = 21 JRA DOI 30	N = 28 JRA DOI 30	N = 22 125 mg BID

	Celecoxib 6 mg/kg/day, 50 mg/5 mL	**Celecoxib 12 mg/kg/day, 100 mg/5mL**	**Naproxen 15 mg/kg/day, 125 mg/5mL**
	(14/20 = 70%) 50 mg BID (100 mg TDD)	**(20/22 = 91%** 100 mg BID (200 mg TDD)	(250 mg TDD)
> 25 kg to ≤ 37 kg	N = 20 JRA DOI 30 **(13/16 = 81%)** 75 mg BID (150 mg TDD)	N = 0	N = 20 187.5 mg BID (375 mg TDD)
> 37 kg to ≤ 50 kg	N = 17 JRA DOI **(11/15 = 73%)** 100 mg BID (200 mg TDD)	N = 0	N = 22 250 mg BID (500 mg TDD)
> 50 kg	N = 0	N = 0	N = 21 500 mg BID (1000 mg TDD)
Abbreviations: kg=kilograms			

The sub-analysis of pooled data in Table 34 demonstrates that efficacy, measured by the JRA DOI 30, is maintained in the 58 patients who received 100 mg to 200 mg/day in the low-dose celecoxib treatment group: JRA DOI 30 = 70% (14/20 patients, > 12 kg to ≤ 25 kg; JRA DOI 30 = 81% (13/16 JRA patients, > 25 kg to ≤ 37 kg) and JRA DOI 30 = 73% (11/15 JRA patients, > 37 kg to ≤ 50 kg)].

There were 20/22 patients > 12 kg to ≤ 25 kg treated with high-dose celecoxib (200 mg/day) and efficacy was maintained as JRA DOI 30 = 91% .There were 0 patients studied in the weight category ≥ 9 to ≤ 12 kg with low-dose celecoxib and 0 patients studied in the weight categories of > 25 kg to ≤ 37 kg, > 37 kg to ≤ 50 kg and > 50 kg, in the high-dose celecoxib group.

Analysis of the primary endpoint, JRA DOI 30, for these 177 patients who received celecoxib as 100 mg/day or 200 mg/day demonstrates persistence of efficacy for both the low-dose celecoxib and high-dose celecoxib treatment groups. Both celecoxib treatment groups achieved non-inferiority to the active comparator, naproxen, by the pre-specified lower limit margin of 0.25 at the 95% confidence interval. See Table 35.

Table 35. Analysis of the Primary Endpoint (JRA DOI 30) in the 12-Week Double-Blind Phase Excluding Patients who received Celecoxib Suspension > 200 mg TDD

		Celecoxib Suspension 6 mg/kg/day		**Celecoxib Suspension 12 mg/kg/day**		**Naproxen Suspension 15 mg/kg/day**	
Celecoxib TDD	**N = Total Pts. Randomized**	**N = Pts.**	**Responders/ N, % Improvement**	**N = Total Pts.**	**Responders/ N, % Improvement**	**N = Total Pts.**	**Responders/ N,% Improvement**
All	242	77	53 / 77 68.83 %	82	66 / 82 80.0 %	83	56 / 83 67.43 %
W/O 600 mg TDD	225	NA	NA	52	52/65 80.0 %	NA	NA

		Celecoxib Suspension 6 mg/kg/day		Celecoxib Suspension 12 mg/kg/day		Naproxen Suspension 15 mg/kg/day	
Celecoxib TDD	**N = Total Pts. Randomized**	**N = Pts.**	**Responders/ N, % Improvement**	**N = Total Pts.**	**Responders/ N, % Improvement**	**N = Total Pts.**	**Responders/ N,% Improvement**
W/O 600, 400 mg TDD	211	NA	NA	42	42 / 51 82.36 %	NA	NA
W/O 600, 400, 300 mg TDD	177	59	40 / 59 67.80 %	35	29 / 35 82.36%	NA	NA
Abbreviations: TDD= total Daily Dose; NA = Not Applicable; mg = milligram; kg = kilogram							

From the analysis of the primary endpoint, the JRA DOI 30, it appears that, regardless of the higher celecoxib doses administered to patients, the efficacy results are persistent across the two celecoxib treatment groups. See Tables 36, 37, and 38. It may be concluded that the high-doses of celecoxib administered in this pediatric trial (higher the adult dose of ~3 mg/kg/day for the indication of RA) were not needed to achieve efficacy in JRA patients.

Table 36. Primary Efficacy Endpoint: JRA DOI 30 (Intent-to-Treat Population), Week 12 Double-Blind Phase, Celecoxib (100 mg to 400 mg TDD)

Treatment Comparisons	**JRA DOI 30, Per Cent Improvement**	**Difference**	**95% CI**
Celecoxib 6 mg/kg/day vs Naproxen 15 mg/kg/day	68.83% vs 67.47%	0.014 (1.40%)	-13.1, 15.8
Celecoxib 12 mg/kg/day vs Naproxen 15 mg/kg/day	80.0% vs 67.47%	0.125 (12.5%)	-1.48, 26.5
Celecoxib 12 mg/kg/day vs Celecoxib 6 mg/kg/day	80.0% vs 68.83%	0.112 (11.2%)	-3.03, 25.4
Abbreviations: CI = Confidence interval;			

Table 37. Primary Efficacy Endpoint: JRA DOI 30 (Intent-to-Treat Population), Week 12 Double-Blind Phase, Celecoxib (100 mg to 300 mg TDD)

Treatment Comparisons	**JRA DOI 30 Per Cent Improvement**	**Difference**	**95% CI**
Celecoxib 6 mg/kg/day vs Naproxen 15 mg/kg/day	69 % vs 68 %	0.149 (14.90%)	-13.1, 15.8

Treatment Comparisons	JRA DOI 30 Per Cent Improvement	Difference	95% CI
Celecoxib 12 mg/kg/day vs Naproxen 15 mg/kg/day	82 % vs 68 %	0.014 (1.40%)	3.52, 29.4
Celecoxib 12 mg/kg/day vs Celecoxib 6 mg/kg/day	82 % vs 69 %	0.135 (13.50%)	-1.20, 28.2
Abbreviations: CI = Confidence interval;			

Table 38. Primary Efficacy Endpoint: JRA DOI 30 (Intent-to-Treat Population), Week 12 Double-blind Phase, Celecoxib (100 mg to 200 mg TDD)

Treatment Comparisons	JRA DOI 30 Per Cent Improvement	Difference	95% CI
Celecoxib 6 mg/kg/day vs Naproxen 15 mg/kg/day	68 % vs 68 %	0.30 (3.00%)	-15.3, 15.9
Celecoxib 12 mg/kg/day vs Naproxen 15 mg/kg/day	83 % vs 68 %	0.154 (15.4%)	-0.70, 31.4
Celecoxib 12 mg/kg /day vs Celecoxib 6 mg/kg/day	83 % vs 68 %	0.151 (15.1%)	-2.20. 32.3
Abbreviations: CI = Confidence interval;			

ADDITIONAL EFFICACY ANALYSES
Celecoxib Suspension, 100 mg to 200 mg Total Daily Dose, [PROPOSED DOSAGE]

Secondary Endpoints
In the subset of 177 patients with JRA treated with celecoxib suspension in doses based on the sponsor's proposed prescribing by weight, descriptive statistics were analyzed for each of the secondary endpoints from the reported observations. See Table 39.

Table 39. Secondary Endpoints: the 6 Core Set Variables of the JRA DOI 30 in the Double-Blind Phase, (Celecoxib 100 mg to 200 mg Total Daily Dose) ITT Population, N=177

Secondary Endpoints: (6 Core Set Variables of the JRA DOI 30)	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
	LS Mean		

Physician's Global Assessment of Disease Activity	17.03	21.31	20.09
Parent's Global Assessment of Overall Well-Being (CHAQ Subsection)	17.56	24.99	23.79
Functional Ability (CHAQ Disability Index)	16.80	22.91	22.53
Number of Joints with Active Arthritis	7.31	6.60	6.80
Number of Joints with Limited Range of Motion	2.86	4.21	3.99
Laboratory Marker of Inflammation (C-Reactive Protein	16.82	11.29	15.07
Abbreviations: LS= Least Squares Mean			

Table 40 Primary Efficacy Endpoint: JRA DOI 50 (Intent-to-Treat Population, N=177)
Week 12, Double-Blind Phase, Celecoxib Suspension 100 mg to 200 mg TDD

Treatment Comparison	**JRA DOI 50, Per Cent Improvement**	**Difference**
Celecoxib 3 mg/kg BID vs Naproxen 7.5 mg/kg BID	-1.2 %	-17.9, 15.9
Celecoxib 6 mg/kg BID vs Naproxen 7.5 mg/kg	7.4 %	-12.4, 25.8
Celecoxib 6 mg/kg vs Celecoxib 3 mg/kg	8.6 %	-12.3, 28.6
Abbreviations : CI=Confidence Interval		

Table 41 Primary Efficacy Endpoint: JRA DOI 70 (Intent-to-Treat Population, N=177)
Week 12, Double-Blind Phase, Celecoxib 100 mg to 200 mg TDD

Treatment Comparison	**JRA DOI 50, Per Cent Improvement**	**Difference**
Celecoxib 6 mg/kg/day vs Naproxen 15 mg/kg/day	-8.8 %	-23.3, 6.9
Celecoxib 12 mg/kg/day vs Naproxen 15 mg/kg/day	1.8 %	-15.9, 21.4
Celecoxib 12 mg/kg/day vs Celecoxib 6 mg/kg/day	10.6 %	-8.1, 30.3
Abbreviations : CI=Confidence Interval		

ADDITIONAL EFFICACY ANALYSES

Methotrexate Treated Patients (celecoxib 100 mg to 600 mg TDD) [Non Pre-Specified Analysis]

Study 195 included a subpopulation of JRA patients taking methotrexate as mono-therapy. Of the total randomized population, 39% (low-dose celecoxib), 35.4% (high-dose celecoxib) and 33.7% (naproxen), also received the DMARD, methotrexate, as co-administration at Baseline. Patients were permitted to take methotrexate at dosages ≤ 1 mg/kg /week with a maximum allowable weekly dose of 40 mg. Patients had to have received a stable dose of methotrexate for at least 8 weeks prior to Screening. The distribution of patients with and without co-administration of methotrexate therapy at baseline was balanced across the three treatment groups. See Table 42.

Hydroxychloroquine, alone or in combination, was the most frequently used DMARD or BRM in the non-methotrexate group. There were 3, 2 and 5 patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, taking hydroxychloroquine. Hydroxychloroquine was the most frequently used DMARD in the methotrexate combination therapy group, with 3, 2 and 2 patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively.

Table 42.
DMARDs and BRMs Used at Baseline for Subgroups, Study 195 (ITT Cohort) (Sponsor Table 1*, p 4 of 64)

SubGroup/ DMARD or BRM Used at Baseline	Celecoxib 3 mg/kg BID 50 mg/5 mL N= 77	Celecoxib 6 mg/kg BID 100mg/5 mL N= 82	Naproxen 7.5 mg/kg BID (125 mg/5 mL) N = 83
Methotrexate,[a] n (%)	30 (39.0)	29 (35.4)	28 (33.7)
Non-methotrexate, n (%)	47 (61.0)	53 (64.6)	55 (66.3)
No DMARD or BRM, n (%)	38 (49.4)	42 (51.2)	40 (48.2)
DMARD, n (%)			
Azathioprine	0 (0.0)	1 (1.2)	0 (0.0)
Hydroxychloroquine Sulfate	3 (3.9)	2 (2.4)	5 (6.0)
Sulfasalazine	1 (1.3)	3 (3.7)	3 (3.6)
BRM, n (%)			
Etanercept	0 (0.0)	1 (1.2)	0 (0.0)
Combination therapy, n (%)			
Azathioprine/Infliximab	0 (0.0)	0 (0.0)	1 (1.2)
Methotrexate/Hydroxychloroquine	3 (3.9)	2 (2.4)	2 (2.4)
Methotrexate/Sulfasalazine	0 (0.0)	0 (0.0)	1 (1.2)
Methotrexate/Etanercept	2 (2.6)	0 (0.0)	1 (1.2)
Methotrexate/Infliximab	0 (0.0)	2 (2.4)	1 (1.2)
Methotrexate/Hydroxychloroquine/Sulfasalazine	0 (0.0)	0 (0.0)	1 (1.2)

BID = Twice daily; BRM = Biological response modifier; DMARD = Disease-modifying anti-rheumatic drug; ITT = Intent-to-treat

[a] Patients for whom methotrexate was the only DMARD or BRM used at baseline
*Source: Study 195 CSR, Table 16 (plus hand tabulation) (from original submission June 20, 2006)

The primary efficacy measure, JRA DOI 30, was applied to this subgroup analysis.
The subgroup analysis used the ITT population (all treated patients): Patients for whom the only DMARD or biological response modifier (BRM) through week 12 was methotrexate, ie, patients receiving methotrexate mono-therapy (methotrexate subgroup), and all other ITT patients, including patients receiving other DMARDs or BRMs (alone or in combination with methotrexate) and patients receiving no DMARDs or BRMs through week 12 (non-methotrexate subgroup).

There is a detectable difference between the responders (JRA 30 DOI) at week 12 in the low-dose celecoxib treatment group without co-administration of methotrexate (confidence Interval [CI] 0.46, 0.75, point estimate of 0.65), compared to the low-dose celecoxib treatment group with co-administration of methotrexate (CI 0.61, 0.92, point estimate of 0.80), with the methotrexate co-administration group demonstrating a higher point estimate.
There is a detectable difference between the responders in the high-dose celecoxib treatment group without co-administration of methotrexate (CI 0.68, 0.91, point estimate of 0.81), compared to low-dose celecoxib with co-administration of methotrexate (CI 0.60, 0.92, with a point estimate of 0.79), with the methotrexate co-administration treatment group demonstrating a higher point estimate.

The JRA 30 DOI responder results, with and without co-administration of methotrexate, do not trend as expected when comparing the two naproxen treatment groups. The naproxen treatment group without methotrexate (CI 0.57, 0.82, point estimate of 0.71) compared to naproxen treatment group with methotrexate co-administration (0.41, 0.78, point estimate of 0.61), demonstrated that the naproxen treatment group with methotrexate has a lower point estimate with the co-administration of methotrexate. See Tables 43 and 44. This is most likely due to the small numbers in this sub-analysis.

Study 195 was not prospectively powered to detect a difference in these subgroups, co-administration, with and without methotrexate. The smaller number of patients in each subgroup, in comparison to the total number of randomized patients (n = 242), explains the wider confidence intervals for the differences demonstrated among the treatment groups. There appears to be no indication that celecoxib would be contraindicated for administration with methotrexate. See Section 7.0 Integrated Review of Efficacy for sub-analysis of safety and co-administration of methotrexate.

Tables 43. JRA 30 Definition of Improvement at Week 12, Double-Blind Phase with Co-Administration of Methotrexate (ITT Cohort; LOCF)

	Methotrexate		
Statistic	**Celecoxib 6 mg/kg/day N = 30**	**Celecoxib 12 mg/kg/day N = 29**	**Naproxen 15 mg/kg/day N = 28**
Point Estimate	0.80	0.79	0.46
Confidence Intervals			

(CI)	0.61, 0.92	0.60, 0.92	0.41, 0.78

Table 44. JRA 30 Definition of Improvement at Week 12, Double-Blind Phase without Co-Administration of Methotrexate (ITT Cohort; LOCF)

	Without Methotrexate		
Statistic	**Celecoxib 6 mg/kg/day N = 47**	**Celecoxib 12 mg/kg/day N = 53**	**Naproxen 15 mg/kg/day N = 55**
Point Estimate	0.65	0.81	0.71
Confidence Intervals (CI)	0.46, 0.75	0.68, 0.91	0.57, 0.82

Analysis of the secondary efficacy measures, the 6 core variables of the JRA 30 DOI (See section 6.1.2), does not demonstrate clinically meaningful differences in trends across these measures, with and without co-administration of methotrexate.

6.1.5 Clinical Microbiology

Clinical microbiology review for celecoxib (approved December 1998) is not applicable in this pediatric supplement submission. Naproxen, the active comparator, is an approved drug for patients with JRA.

6.1.6 Efficacy Conclusions

Study 195 was the Phase 3 pivotal study of celecoxib oral suspension in a 12-week, randomized, double-blind, active-controlled, parallel-group, multicenter, non- inferiority study comparing the efficacy and safety of low-dose celecoxib and high-dose celecoxib to naproxen suspension, in JRA patients with an optional 12-week open-label phase with only high-dose celecoxib. Two different celecoxib suspensions were studied, 50 mg/5 mL and 100 mg/5 mL, for the low-dose and the high-dose celecoxib administration, respectively.

This medical reviewer concludes that the low-dose celecoxib and the high-dose celecoxib achieve non-inferiority to the active comparator, naproxen. The pre-specified criterion for the non-inferiority trial design was claimed if the lower limit of the 95% 2-sided confidence interval for the difference in the percent responders (celecoxib – naproxen) was above -25%.

The primary endpoint for efficacy was the JRA DOI 30, a composite score of 6 core variables. The high-dose celecoxib treatment group had numerically better treatment effect than did the low-dose celecoxib treatment group, though not statistically significantly different as analyzed by the JRA DOI 30. The proportion of patients achieving the **JRA DOI 30** criterion over the **12 week double-blind phase** was **69%, 80% and 67%,** for the **low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively.** The difference at 12-week (Final visit) in the double-blind phase for low-dose celecoxib – naproxen was +1.36% (-13.08%, 15.80%) with a p-value of 0.8535, and the difference for high-dose celecoxib – naproxen, was +13.02% (-0.22%, 26.25%) with a p-value of 0.0568.

Efficacy, as measured by the JRA DOI 30, was maintained at the proposed celecoxib total daily dose of 100 mg or 200 mg/day compared. **Some children in Study 195 received celecoxib doses in excess of 200 mg per day, for example > 400 mg to 600 mg/day. These are higher than the labeled adult dose for RA, a starting dose of 100 mg BID (200 mg/day) to a maximum of 200 mg BID (400 mg/day). The average adult (60-70 kg) would receive celecoxib as approximately 3.3 mg/kg/day starting dose, which is less than both celecoxib treatment dosages administered in Study 195. The proposed dose scheme demonstrates that the smallest weight patients would receive the highest doses of celecoxib.** This is a concern as the **safety profile trends with increased adverse events with high-dose celecoxib.**

The non-inferiority margin has been questioned as to the rigor of this pre-specified margin in the target JRA population, young and older children and adolescents with JRA. This medical reviewer has over 15 years clinical experience with naproxen suspension in the care of JRA patients with all onset course-types and of all pediatric ages and has observed naproxen to be consistently efficacious in polyarticular and pauciarticular. The non-inferiority margin as defined in Study 195 is consistent with this reviewer's clinical experience and therefore is acceptable.

The proportion of JRA patients who discontinued the double-blind phase of Study 195 due to adverse events was highest in the high-dose celecoxib group (7 patients), and equal in the low-dose celecoxib and in the naproxen treatment groups (4 patients each treatment group). See Section 7.1 Safety for the details of these specific adverse events. Discontinuations due to lack of efficacy were 2, 1, and 4 patients in the low-dose celecoxib suspension, high-dose celecoxib suspension, and naproxen suspension treatment groups.

Secondary endpoint and other evaluations were the Parent's Assessment of Child's Arthritis Pain (visual analogue scale [VAS]), CHAQ subsection, and the Pediatric Quality of Life Inventory, as well as, various definitions of improvement for use in the JRA population (JRA DOI-50; JRA DOI-70 and JRA DOI-30 in pauciarticular and polyarticular JRA, separately).

Analysis of the secondary endpoints demonstrates that both the low-dose and the high-dose celecoxib suspension are non-inferior to naproxen suspension in the assessment of the 6 core set variables in the double-blind phase. Assessment of the individual component, the number of joints with limited range of motion, demonstrates statistical significant differences in the double-blind phase in favor of the high-dose celecoxib suspension at Week 8 with a difference of 1.45 [0.42, 2.49], p=0.0062, and at Week 12 with a difference of 1.44 [0.25, 2.63], p=0.0181.

The secondary endpoints for the analysis in the open-label phase demonstrate a favorable trend for the high-dose celecoxib over the low-dose celecoxib (based on the original treatment group randomization) but without a detectable statistical difference. In the open-label phase, the only secondary endpoint where the low-dose celecoxib trended more favorably than the high-dose celecoxib was in the assessment of the Pediatric Quality of Life Inventory, Physical Health Summary of the Child's Self-Report, as measured by the mean change from Baseline to Week 24, 12.13 (SD 20.74).

In the 12-week double-blind phase, the response rates for the **JRA DOI 50** were **56%, 61% and 55%,** and for the **JRA DOI 70** were **25%, 37% and 33%**, respectively for the low-dose celecoxib, high-dose celecoxib and the naproxen treatment groups.

By sub-group analysis, the percentage of patients with pauciarticular JRA who achieved the JRA DOI 30 criterion at Week 12 double-blind phase was 76%, 78% and 79% for low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively. In the sub-group analysis of JRA, by polyarticular or pauciarticular course, there was a detectable difference with the JRA DOI 30 response rate ($p = 0.0110$) for polyarticular course JRA treated with high-dose celecoxib at Week 12 compared to the naproxen treatment group. The low-dose celecoxib treatment group demonstrated non-inferiority compared to naproxen treated patients. The study arms were balanced for gender, age and JRA type course, considering the overall higher incidence of JRA in girls than in boys.

The limitations for efficacy in Study 195 are the inadequate amount of patient data to assess *efficacy* and *safety* of celecoxib suspension of the smallest weight patients ≥ 10 kg to ≤ 12 kg and the heaviest patients > 50 kg. There were 0 (zero) patients studied with weight ≤ 12 kg in the low-dose celecoxib group and 2 patients studied in this same weight category in the high-dose celecoxib group. The data submitted is insufficient to adequately assess *efficacy and safety* at the proposed dosage of 100 mg in the smallest weight patients and 200 mg in the patients > 50 kg. See Section 7.1 Safety for additional explanation of this rationale.

There were 88 of 159 randomized patients received celecoxib in a proposed total daily dose of 100 mg or 200 mg/day. (See Table 34) There were 58 patients in the low-dose celecoxib group and 30 patients in the high-dose celecoxib group.

In the low-dose celecoxib groups, the efficacy outcome, by the JRA DOI 30, was as follows:

- 14/20 patients (> 12 kg to ≤ 25 kg) achieved 70% JRA DOI 30;
- 13/16 patients (>25 kg to ≤ 37 kg) achieved 81% JRA DOI 30 and
- 11/15 patients (> 37 kg to ≤ 50 kg) achieved 73% JRA DOI 30.

In the high-dose celecoxib groups, the efficacy outcome, by the JRA DOI 30, was as follows:

- 20/22 patients (> 12 kg to ≤ 25 kg) achieved 91% JRA DOI 30.

There were 0 patients in the weight range > 25 to ≤ 50 kg who received 200 mg/day. See Table 34. Therefore, efficacy of celecoxib is maintained by the non pre-specified pooled sub-group analysis in patients > 12 kg to ≤ 50 kg, with the proposed doses, 100 or 200 mg/day. **The pediatric doses (100 mg/day or 200 mg/day) corresponding to 4 mg/kg/day up to 10 mg/kg/day are higher (in mg/kg/day) than the labeled adult doses (200 mg/day or 400 mg/day) for the indication of RA (~3.3 mg/kg/day).**

The sponsor proposes to use a 50 mg capsule as a sprinkle onto applesauce for pediatric patients unable to swallow an intact capsule. Adult pharmacology studies with a 50 mg capsule were submitted with the original NDA 20-998 for celecoxib (approved December 31, 1998) and include limited adult data with 50 mg capsule. The 50 mg capsule was not used in Study 195.

The sponsor explains that manufacturing an oral suspension was not possible in large quantity. The issue of good faith effort for the production of a suspension formulation remains to be clarified by the CMC review team. See the CMC review by Ramesh Raghavachari, PhD and Stuart Zimmerman, PhD.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety and tolerability of celecoxib in patients with JRA was assessed by review of all safety parameters, physical examinations, growth parameters, vital signs, weight, laboratory safety and reporting of adverse events. The safety population was defined as all patients, subjects and participants who received at least one dose of study drug medication (pharmacokinetic and clinical studies) and includes the adverse events reported up to 28 days after the last dose of study medication. Adverse events that were reported more than 28 days after the last dose of study medication were excluded by the sponsor. The safety profile of celecoxib in adult patients was used as a comparison for adverse events reported from the pediatric and adult patients in Supplement 021.

SAFETY REVIEW
The safety review was conducted from all adverse events reported in the clinical pharmacology Studies 088, 1162, 1202 and Phase 3 pivotal Study 195, including the adult RA clinical investigations reported in RR-049. An Integrated Safety Summary (ISS), per se, was not submitted.

Patient Exposure: Pre-Specified Dosing
Two-hundred and forty-two JRA patients were randomized into the 12-week double-blind phase. Two-hundred and twelve of these patients completed the double-blind phase and 202 of these patients entered the open-label phase of Study 195. See Table 3 in Section 6.1, Efficacy. In the double-blind phase and in the open-label phase, patients with JRA between 2 years to 16 years of age received a suspension formulation of the study medication, celecoxib, or the active comparator, naproxen, dosed by Baseline body weight. See Table 2, Section 6.1 Efficacy. Patients were allocated to the low-dose celecoxib, high-dose celecoxib and to naproxen treatment groups.

As noted by the sponsor and this medical reviewer, during the 12-week double-blind phase, a total of 77 patients in the low-dose celecoxib group, 82 patients in the high-dose celecoxib group, and 83 patients in the naproxen group, had exposures to study medication of 17, 18 and 19 patient-years, respectively. Most patients in the double-blind phase took study mediation for at least 60 days. In the open label phase, most patients took study medication for at least 85 days. Exposure in patient-years to any dose of celecoxib was 80, with 88 (38%) of patients treated for > 168 days. See Table 45 and 46.

Table 45. Duration of Exposure, Double-Blind Phase, Study 195
(Sponsor Table 17, page 70 of 4701)

	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
Duration in Days			
1-29	8 (10%)	6 (7%)	2 (2%)
30-59	1 (1%)	5 (6%)	5 (6%)
60-93	65 (84%)	71 (87%)	69 (83%)
> 93	3 (4%)	0 (0.0%)	7 (8%)
Number Treated	77	82	83
Patient-Years of Exposure	17	18	19
Data Source Table 13; Table19.1			

Table 46. Duration of Exposure, Open-Label Phase, Study 195
(Sponsor Table 18, page 71 of 4701)

	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
Duration in Days			
1-29	1 (2%)	2 (3%)	1 (1%)
30-59	0 (0%)	2 (3%)	1 (1%)
60-84	30 (48%)	29 (41%)	25 (36%)
85-114	31 (50%)	37 (53%)	42 (60%)
>114	0 (0%)	0 (0%)	1 (1%)
Number Treated	62	70	70
Patient-Years of Exposure	14	16	16
Source Table 13; Table 19.2			

Patients were allocated to each treatment group with doses calculated by the patient's weight at Baseline. The total daily dose did not change during the double-blind phase even if the patient's weight changed. See Table 47-A.

As explained by the sponsor, "the target dose levels are approximate because a fixed volume of study drug suspension was given over a range of weights within the pre-specified weight ranges. A patient's dose may exceed celecoxib 6 mg/kg/day or 12 mg/kg/day for individuals at the lighter end of a given weight range. Celecoxib oral suspension was provided as either 50 mg/5 mL (low-dose) or 100 mg/5 mL (high-dose)". The actual range of doses delivered in the 3 treatment arms was based upon the patient's weight within specific weight categories. See Table 47-B. Study medication was dispensed at Baseline and Weeks 4 and 8 during the double-blind treatment phase.

Table 47-A. Dosage Based on Weight Ranges (Note: Fixed Volume of Study Medication)
(Sponsor Table 5, page 43 of 4701)

Weight	Celecoxib Low-Dose Suspension (3 mg/kg BID)	Celecoxib High-Dose Suspension (6 mg/kg BID)	Naproxen Suspension (7.5 mg/kg BID)
9-12 kg	25 mg BID (50 mg TDD)	50 mg BID (100 mg TDD)	62.5 mg BID (125 mg TDD)
13-25 kg	50 mg BID (100 mg TDD)	100 mg BID (200 mg TDD)	125 mg BID (250 mg TDD)
26-37 kg	75 mg BID (150 mg TDD)	150 mg BID (300 mg TDD)	187.5 mg BID (375 mg TDD)
38-50 kg	100 mg BID (200 mg TDD)	200 mg BID (400 mg TDD)	250 mg BID (500 mg TDD)
>50 kg	150 mg BID (300 mg TDD)	300 mg BID (600 mg TDD)	500 mg BID (1000 mg TDD)

Note: Celecoxib Low-Dose Suspension = 50 mg/5 mL; Celecoxib High-Dose Suspension = 100 mg/5 mL; Naproxen Suspension = 125 mg/5 mL.
Abbreviations: BID = Twice Daily; TDD = Total Daily Dose; mg = Milligram; kg = Kilogram; mL = Milliliter.

The range of doses in the low-dose celecoxib group were 3 to 7.6 mg/kg/day and in the high-dose celecoxib group were 6 - 15.4 mg/kg/day. A fixed-volume dosing scheme is associated with a range of actual administered doses. See Table 47-B and 47-C. See the Clinical Pharmacology review by Srikanth Nallani PhD and Atul Bhattaram, PhD.

Table 47-B. Dose Ranges Delivered Based upon the Patient's Weight
(Sponsor table 6, page 43 of 4701)

Weight	Dose Ranges Celecoxib 3 mg/kg BID	Dose Ranges Celecoxib 6 mg/kg BID	Dose Ranges Naproxen 7.5 mg/kg BID
9-12 kg	2.1-2.8 mg/kg BID	4.2-5.6 mg/kg BID	5.2-6.9 mg/kg BID
13-25 kg	2.0-3.8 mg/kg BID	4.0-7.7 mg/kg BID	5.0-9.6 mg/kg BID
26-37 kg	2.0-2.9 mg/kg BID	4.1-5.8 mg/kg BID	5.1-7.2 mg/kg BID
38-50 kg	2.0-2.6 mg/kg BID	4.0-5.3 mg/kg BID	5.0-6.6 mg/kg BID
>50-100 kg	1.5-2.9 mg/kg BID	3.0-5.9 mg/kg BID	5.0-9.8 mg/kg BID

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: BID = Twice Daily; mg = Milligram; kg = Kilogram; mL = Milliliter.

Table 47-C. Summary of Celecoxib Oral Clearance (CL/F), Steady State Area under the Plasma Concentration-Time Curve [$AUC_{(0-12)}$], and % Responders (Sponsor Table 14, RR-049, page 50 of 238)

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.

Patient Exposure: Actual Dosing [NON PRE-SPECIFIED ANALYSIS]

As demonstrated in Table 47-D, the majority of patients in the low-dose celecoxib group (80%; 64 of 77 patients) received ≥ 4 to < 6 mg/kg/day and the majority of patients in the high-dose celecoxib group (76%; 63 of 82 patients) received ≥ 8 mg to < 10 mg/kg/day. In the open-label phase, the majority of patients (56%; 114 of 202 patients) in the single-arm treatment group of high-dose celecoxib received ≥ 8 to < 10 mg/kg/day.

As cited above, fixed-volume dosing results a range of study drug doses within each weight category. **Actual doses that are 25-30% above or below an intended prescribed celecoxib dose for pediatric patients create a safety risk. Based on the safety profile of celecoxib in this limited study, doses that may not be accurate, according to patient weight, may have clinically meaningful implications for safety.**

The proposed dose scheme demonstrates that the smallest weight patients would receive the highest doses of celecoxib. This is a concern as the **safety profile trends with increased adverse events with the higher celecoxib dose. The proposed pediatric dose scheme includes a dose range which would be higher than the approved dose range (in mg/kg/day) for adult**

RA patients. The calculated dose for some of the patients in Study 195 was as high as 600 mg/day.

Table 47-D. Protocol Celecoxib Dosage Compared to Actual Celecoxib Dosage Received, Study 195*.

Actual Dosage Administered	**Celecoxib 6 mg/kg/day Double-Blind N=77**	**Actual Dosage Administered**	**Celecoxib 12 mg/kg/day Double-blind N= 82**	**Celebrex 12 mg/kg/day Open-Label N=202**
≥ 6 to ≤ 7 mg/kg/ay	8 (10%)	≥ 12 to14 mg/kg/day	8 (9%)	15 (7%)
≥ 5 to < 6 mg/kg/day	28 (36%)	≥ 10 to <12 mg/kg/day	25 (30%)	54 (26%)
≥ 4 - < 5 mg/kg/day	34 (44%)	≥ 8 to < 10 mg/kg/day	38 (46%)	60 (29%)
< 4 mg/kg/day	5 (6%)	< 8 mg/kg/day	9 (11%)	2 (<1%)
Abbreviations: kg=kilograms; mg=milligrams; *Note: Data was analyzed from a pdf file in response to an Information Request to the sponsor on September 6, 2006				

7.1.1 Deaths

There were no deaths reported in the Study 195, the two clinical pharmacokinetic studies, CMC study or the adult population PK study.

Deaths Reported, Consult from the Division of Drug Risk Evaluation
The Adverse Event Reporting System (AERS) database was searched for all serious and non-serious pediatric adverse events reported between 12/31/98 and 08/10/06. There was one fatal case reported in a 15-year-old male who began taking celecoxib (dose unknown) for pain following anterior cruciate ligament reconstruction of the left knee, and committed suicide 2 to 3 weeks later. The treating physician stated that the suspect medication was "Celebrex, claimed by the family" but the records did not indicate that he was prescribed celecoxib. The physician is also to have stated that celecoxib sample was given but not recorded. Both depression and suicide are labeled events for celecoxib. Given the information in the case, the relationship between the reported event and celecoxib was unclear. The role of celecoxib could not be excluded.

Postmarketing Deaths
Celecoxib is currently not approved for use in the pediatric population. See comments above from the consult from the Division of Drug Risk Evaluation.

7.1.2 Other Serious Adverse Events

There were 9 patients who experienced serious adverse events (SAEs) in Study 195. In the 12-week double-blind phase, 5 patients had SAEs, 3 patients in the low-dose celecoxib and 2 patients in the high-dose celecoxib treatment groups. In the 12-week open-label phase, 4 patients experienced SEAs, 1 patient in the low-dose celecoxib group originally (double-blind phase) prior to receiving high-dose celecoxib in the open-label extension; and in 3 patients in the

high-dose celecoxib group in both the double-blind and the open-label phase. The following summaries are examples of patients who experienced SAEs in Study 195. See Table 48.

Patient 1045, a 15-year-old boy, experienced severe epigastric pain within the first day of receiving low-dose celecoxib suspension (4.8 mg/kg/day). This GI experience could be causally related to celecoxib suspension.

Patient 1176, a 6-year-old boy, suffered a severe flare of asthma within 4 hours of receiving high-dose celecoxib suspension (10 mg/kg/day) on the first day of study drug treatment. There was no prior history of aspirin or NSAID sensitivity in this patient. The celecoxib label carries a warning for individuals with preexisting asthma that celecoxib should not be administered to patients with known aspirin sensitivity and should be used with caution in patients with preexisting asthma. The serious adverse event, acute flare of asthma, could be causally related to celecoxib.

Patient 1088, a 14-year-old girl, experienced overdose of erythromycin and celecoxib, with nausea and vomiting, both of which may be causally related to these GI events. She was receiving low-dose celecoxib suspension as (5 mg/kg/day).

Table 48. Patient Summaries, Serious Adverse Events: Double-Blind and Open-Label Phase

Patient #, Age, Gender	Treatment Group, Dosage, TDD	SAE, Day of Onset, Concomitant Meds	Comments
DOUBLE-BLIND PHASE			
1045 15 yrs., F	**Low-dose celecoxib** 6 mg/kg/day **(300 mg TDD)** (Pt. received ~4.8 mg/kg/day, based on wt. 62.5 kg at Baseline)	Severe epigastric pain (Day 1) GI event, possible study drug rel. (+)	Recovered
1303 11 yrs., M	**Low-dose celecoxib** 6 mg/kg/day **(300 mg TDD)** (Pt. received ~5.6 mg/kg/day, based on wt of 53 kg in the DB, then 10.9 mg/kg/day in the OL)	Acute viral illness (Day 84); hospitalized; Concomitant meds: Paracetamol PRN for headaches. Possible study drug rel (-)	Recovered
1351 8 yrs., F Systemic JRA	**Low-dose celecoxib** 6 mg/kg/day **(300 mg TDD)** (Pt received ~4.7 mg/kg/ day, based on wt of 23 kg at Baseline)	Acute CMV hepatitis; hospitalized (Day 29) hospitalized; nausea, vomiting, altered mental status, fever, elevated hepatic enzymes. Concomitant meds: MTX, ranitidine, piroxicam, folic acid, acetaminophen, multivitamin. GI events, possible study drug rel (-)	Recovered

Patient #, Age, Gender	Treatment Group, Dosage, TDD	SAE, Day of Onset, Concomitant Meds	Comments
1176 6 yrs., M	**High-dose celecoxib** 12 mg/kg/day **200 mg TDD** (Pt received ~10 mg/kg/ day, based on wt of 20 kg at Baseline)	Severe exacerbation of asthma 4 hrs post first dose (Day 1); Concomitant meds: MTX, Ventolin, Seretide, Flutide, Singulair, folic acid, Calcium supplements. Possible study drug rel (+)	Recovered
1326 13 yrs., M	**High-dose celecoxib** 12 mg/kg/day **(600 mg TDD)** (Pt received ~6.5 mg/kg/day, based on wt of 92.7 kg at Baseline)	Worsening JRA pain, swelling of ankles/tarsus on (Day 57). Concomitant meds: etanercept, prednisone. Possible study drug rel (-)	Recovered
OPEN-LABEL PHASE			
1088 14 yrs., F	**Low-dose celecoxib** 6 mg/kg/day **(300 mg TDD)** to **High-dose celecoxib** 12 mg/kg/day **(600 mg TDD)** (Pt. received ~5 mg/kg/ day, based on wt. of 57.5 kg; then ~10 mg/kg/day based on wt. 59.5kg)	**Severe epigastric pain** and vomiting post intentional overdose of erythromycin 250 mg (10 tablets) and celecoxib 100 mg/ 5mL suspension (200 mL) (Day 150). No concomitant meds. GI events, possible study drug rel (+), in addition to erythromycin.	Recovered, except elevated CK believed to be secondary to physical exercise.
1044 15 yrs., M Systemic onset JRA	**High-dose celecoxib** 12 mg/kg/day **(300 mg TDD)** to **High-dose celecoxib** 12 mg/kg/day **(400 mg TDD)** (Pt received ~8 mg/kg/ day based on wt 37.8 kg in DB, then ~9.7 mg/kg/ day based on wt. 40.9 kg at Week 12 visit)	Chest pain, inflammatory myopericarditis, flare of systemic features of JRA (Day 101). Concomitant meds: MTX, prednisone, calcium sulfate, calcium, vitamin D, ferrous sulfate. Possible study drug rel (+)	(Note: Past hx of myopericarditis) DIC panel D-Dimer 12,980 (ULN 400 µg/L), fibrinogen 5.70 g/L (normal 2.0-4.0 g/L); fibrinogen degradation products ≥ 80 to < 160 µg/mL (reference range < 5 µg/mL). Echo-cardiogram was normal.
1161 12 yrs., M	**High-dose celecoxib** 12 mg/kg/day **(400 mg TDD)** to **High-dose celecoxib** 12 mg/kg/day **(300 mg TDD*)** *Note: Pts. weight	Nausea (Day 129), vomiting, dehydration; malaise, fever, arthralgia. Lower respiratory tract infection; hospitalized (Day 132); CXR w/ alveolar peribronchial infiltrates, left hilar enlargement. Discharge diagnosis primary pulmonary tuberculosis. Concomitant meds: MTX,	Treated for TB.

Patient #, Age, Gender	Treatment Group, Dosage, TDD	SAE, Day of Onset, Concomitant Meds	Comments
	decreased from Baseline to Week 12/Final visit. (Pt received ~10 mg/kg/ day based on wt 38.5 kg in DB Phase; then received 8.4 mg/kg/day, based on wt of 35.6 kg at Week 12.)	prednisone, folic acid, calcium carbonate, choroquine. GI events, possible study drug rel (+)	
1225 7 yrs., F	**High-dose celecoxib** 12 mg/kg/day **(300 mg TDD)** remained on same dosage. (Pt received ~10.5mg/kg/day, based on wt of 28.2 kg; then ~10 mg/kg/day based on wt. 30 kg)	Severe lymphadenopathy, pyrexia, sore throat NOS, mild torticollis (Day 109); hospitalized. No concomitant meds. Possible study drug rel (-)	Celecoxib temporarily discontinued on Day 109; resumed on Day 111.
Abbreviations: CMV = cytomegalovirus; TDD = Total Daily Dose; PRN = as needed; MTX = methotrexate; hx=history; SAE=Serious adverse events; Possible study drug rel (+/-) = Possible study drug relationship (+) or (-).			

Systemic Onset JRA

There were 4 (5%), 10 (12%) and 8 (9%) patients who had systemic onset JRA (with currently inactive systemic features) randomized to the in low-dose celecoxib, high-dose celecoxib and the naproxen treatment groups, respectively. Overall, there appears to be a safety signal for patients with systemic onset JRA with an overall experience of 23% experiencing severe or serious adverse events. See Table 48. There were **5 patients (23%) with systemic onset JRA who experienced severe or serious AEs, 1 of 4 (25%), 2 of 10 (20%), and 2 of 8 (25%) patients, in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively.** Examples of the safety experiences in the systemic onset JRA sub-group are as follows:

> Patient # 1351, an 8-year-old girl, experienced acute cytomegalovirus hepatitis and required hospitalization due to nausea, vomiting, altered mental status, fever and elevated hepatic enzymes (> 3 x ULN) while receiving low-dose celecoxib (4.7 mg/kg/day). Her final diagnosis was acute CMV hepatitis. The GI adverse events could be causally associated with the CMV hepatitis, flare of her systemic JRA features or could be causally related to celecoxib, which is associated with elevation of hepatic enzymes and is cited in the celecoxib label. This patient was concomitantly taking methotrexate, which is also associated with elevated hepatic enzymes and GI symptoms of nausea and vomiting. Her GI experiences could be causally related to celecoxib. A DIC panel demonstrated normal fibrinogen (2.60 g/L, ULN 4.0 g/L), FDP of ≥ 40 and < 80 (ULN < 5 mg/mL), and D-dimer of 6, 180 mg/L (ULN 499 mg/L). This reviewer notes that the etiology of the abnormal FDP and D-dimer may be related to the altered synthesis and metabolism of coagulation factors due to the CMV hepatitis or to the systemic JRA. A flare of JRA cannot be excluded in this patient.

Patient # 1075, a 10-year-old girl, experienced severe gastritis and mild diarrhea. She received high-dose celecoxib treatment.

Patient # 1044, a 15-year-old male with systemic JRA, randomized to the high-dose celecoxib treatment group, experienced fever, chest pain, and myopericarditis. His DIC panel revealed a D-dimer of 12,980 mg/L (ULN 499 mg/L), fibrinogen of 5.70 g/L (ULN 4.0 g/L) and Fibrinogen Degradation Products (FDP) of ≥ 80 and < 160 mg/mL (ULN, 5 mg/mL), consistent with a flare of systemic features of JRA.

Patients # 1161, a 12-year-old male, randomized to the high-dose celecoxib, developed a lower respiratory tract infection which was later diagnosed as primary pulmonary tuberculosis.

Patient # 1211, a 4-year-old girl, experienced a severe pruriginous allergic reaction on her face and hands on Day 1 of high-dose celecoxib treatment.

Patient # 1343, a 10-year-old girl, experienced severe exacerbation of JRA (not systemic features) with +2 proteinuria and too numerous to count red blood cells in her urine. She received naproxen suspension (~ 12 mg/kg/day).

7.1.3 Dropouts and Other Significant Adverse Events

Severe Adverse Events
There were 44 severe adverse events reported in the double-blind phase and 14 severe adverse events reported in the open-label phase of Study 195. The **most common severe adverse event** in the double-blind phase across the three treatment groups were **gastrointestinal (GI) as upper abdominal pain** followed by **headache NOS**. There was one report of dizziness, severe arthralgia, exacerbation of juvenile rheumatoid arthritis, and severe pain in a limb. There were a total of **22 severe adverse events in the low-dose celecoxib group, and 11 SAEs in both the high-dose celecoxib and in the naproxen, in the double-blind phase.**

Gastrointestinal; musculoskeletal, connective tissue and bone; and **general disorders and administration site conditions** had the **highest number of severe adverse events** in the **low-dose celecoxib group**, double-blind phase. The **nervous system** was on the only body system in which the **naproxen group had more severe adverse events (3 events) compared to the low-dose celecoxib (2 events) and the high-dose celecoxib (1 event).**

There were 10 GI severe adverse events in the low-dose celecoxib group compared to 1 event in the high-dose celecoxib group and 3 in the active comparator group, naproxen. There were 3 severe adverse events in the general disorders and administration site conditions in the low-dose celecoxib group compared to 1 severe adverse event in the high-dose celecoxib group and 1 severe adverse event in the naproxen group. In the body system, musculoskeletal, connective tissue and bone disorders, there were 3 severe adverse events in the low-dose celecoxib group compared to 1 severe adverse event in the high-dose celecoxib group and 2 severe adverse events in the naproxen group. Elevated creatinine phosphokinase was reported in 1 patient in the

low-dose celecoxib group and hematuria was reported in the high-dose celecoxib group. See Table 49.

Table 49. Severe Adverse Events: Double-Blind Phase, Study 195

AE System Organ Class	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day	Total severe adverse events
Gastrointestinal	10	1 (abdominal pain)	3	14
Infections and Infestations	1 (tonsillitis)	1 (urinary tract infection)	1	3
Respiratory, Thoracic, Mediastinal Disorders	0	1 (asthma)	0	1
General Disorders and Administration Site Conditions	3 (2 pyrexia; chest pain)	1 (pyrexia)	1	5
Musculoskeletal, connective Tissue and Bone Disorders	3 (arthralgia, pain in limb)	1 (arthritis)	2	6
Nervous System Disorders	2 (headache)	1 (headache)	3	6
Skin and Subcutaneous Tissue Disorders	1 (ingrown nail)	0	1	2
Immune	0	2 (hypersensitivity)	0	2
Investigations	1 (↑CK)	1 (hematuria)	0	2
Injury and Poisoning	1 (sunburn)	1 (laceration)	0	2
Eye Disorders	0	1 (conjunctivitis)	0	1
Total	**22**	**11**	**11**	**44**

In the **open-label phase**, the total number of **severe adverse events was 6, 4 and 4** in the **high-dose celecoxib, low-dose celecoxib, and naproxen treatment groups, respectively.** The most frequently reported severe adverse events were in the **musculoskeletal, connective tissue and bone disorders** (4 severe adverse events), **nervous system** (3 severe adverse events), and **immune system** (2 severe adverse events). There were 2 GI severe adverse events, 1 severe adverse event of pyrexia, 1 severe adverse event of a cardiac disorder (myopericarditis), and 1 severe adverse event of lymphadenopathy only reported in the high-dose celecoxib group; there were no severe adverse event in the corresponding body systems in either of the other two study groups. The nervous system had 1 severe adverse event in each of the 3 treatment groups. There were 0 severe adverse events in the body systems of infections and infestations; respiratory, thoracic, mediastinal disorders; and skin and subcutaneous tissue disorders. Two severe adverse events reported as hypersensitivity reactions were reported in the open-label phase, 1 in the low-dose celecoxib group and 1 in the naproxen group. See Table 50.

Table 50. Severe Adverse Events, Open-Label Phase, Study 195

AE System Organ Class	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day	Total
Gastrointestinal	0	2 (gastritis, sore throat)	0	2
Infections and Infestations	0	0	0	0
Respiratory, Thoracic, Mediastinal Disorders	0	0	0	0
General Disorders and Administration Site Conditions	0	1 (pyrexia)	0	1
Musculoskeletal, Connective Tissue and Bone Disorders	2	0	2 (arthralgia, neck pain)	4
Nervous System Disorders	1	1 (headache)	1 (headache)	3
Skin and Subcutaneous Tissue Disorders	0	0	0	0
Immune System	1 (hypersensitivity)	0	1 (hypersensitivity)	2
Cardiac Disorder	0	1 (myopericarditis)	0	1
Blood and Lymphatic System Disorder	0	1 (lymphadenopathy)	0	1
Total	**4**	**6**	**4**	**14**

Pediatric Patients

Two-hundred and forty-two patients were randomized in the 12-Week double-blind phase of Study 195. Two-hundred and twelve patients (87.6%) of 242 patients completed the 12-Week phase. Of these 212 patients (87.6%), 202 patients entered the open-label extension phase and 195 (96.5%) completed the open-label phase. See Table 3.

Table 51. Adverse Events Causing Withdrawal: Double-Blind Phase, Study 195
(From sponsor Table 21.1, pages 245-246 of 4701)

System Organ Class Adverse Event (MedDRA)	JRA Treatment Groups		
	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
Any Event (Sponsor)	3	7	3
Any Event (Reviewer)	4	7	4
GI	**3**	0	**4**
Abdominal Pain NOS	1	0	0
Abdominal pain upper	0	0	2
Dysphagia	1	0	0
Nausea	0	0	1
Esophageal pain	1	0	0
Vomiting NOS	0	0	1
Immune System	0	**1**	0
Hypersensitivity NOS	0	1	0
Infections and			

System Organ Class Adverse Event (MedDRA)	JRA Treatment Groups		
	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
Infestations	**1**	0	0
Hepatitis cytomegalovirus	1	0	0
Laboratory Investigations	0	**3**	0
Hematuria present	0	1	0
LFT NOS abnormal	0	1	0
Transaminase NOS increased	0	1	0
Musculoskeletal, CT, Bone Disorders	0	**1**	0
JRA (flare of systemic features)	0	1	0
Respiratory, Thoracic, Mediastinal Disorders	0	**1**	0
Asthma NOS	0	1	0
Skin, Subcutaneous Tissue Disorders	0	**1**	0
Rash, generalized	0	1	0
Abbreviations: CT=Connective Tissue Disorder			

Table 52. Adverse Events Causing Withdrawal to Week 24/End of Open-Label Phase
(From sponsor Table 21.2, page 247-248 of 4701)

System Organ Class Adverse Event (MedDRA)	JRA Treatment Groups		
	Celecoxib 6 mg/kg/day	Celecoxib 12 mg/kg/day	Naproxen 15 mg/kg/day
Any Event (Sponsor)	**1**	**2**	**1**
Any Event (Reviewer)	**1**	**2**	**3**
Cardiac Disorders	0	**1**	0
Myopericarditis	0	1	0
GI	0	**1**	**1**
Gastritis NOS	0	1	0
Vomiting NOS	0	0	1
Immune System	0	0	**1**
Hypersensitivity NOS	0	0	1
Infections, Infestations	0	0	**1**
Gastroenteritis	0	0	1
Skin, Cutaneous Tissue Disorders	**1**	0	0
Dermatitis Allergic	1	0	0

Adult Patients

In the adult cohort of Study 195 (RR-049), celecoxib suspension was administered as 400 mg/day (200 mg BID) for 14 days. There were 2 adult patients who withdrew secondary to a total of 3 adverse events. See Table 53. Patient # 5010, a 79-year-old female, experienced

dizziness and mild diarrhea on Day 2 of celecoxib treatment. Both these adverse events were caused as possibly related to the study medication. Medication was discontinued on the same day and she was withdrawn from the study on Day 9. Patient # 5019, a 75-year-old female, experienced urticaria (moderate severity) on Day 15. Her last dose of celecoxib was received on Day 14. This patient was withdrawn from the study. The urticaria could be casually related to the study drug, celecoxib.

Table 53. Adverse Events Causing Withdrawal in Adult Patients: Population PK Study

Patient #, Age, Gender, Baseline Dx	Adverse Event Celecoxib Suspension 200 mg BID	Comments
# 5010, 79 yr old F, RA	Dizziness and diarrhea (mild) on Day 2; medication discontinued; events resolved on Day 9. Concomitant meds: estrogen, glucosamine, chondroitin, acetaminophen. Possible study drug rel (+)	Resolved on Day 9
# 5019, 75 yr old F, RA	Urticaria (moderate severity) on Day 15; last dose of study med received on Day 14. Concomitant meds: Colace, Metamucil, vitamins, minerals, aspirin, quinine. Possible study drug rel (+)	Resolved on Day 36

7.1.3.1 Overall profile of dropouts

Dropouts Due to SAEs

Pediatric Patients

There were 9 patients reported by the sponsor who dropped out of Study 195 due to SAEs. Four of these 9 patients in the double-blind phase were randomized to receive low-dose celecoxib. See Table 50. See Section 7.1.3.2 Adverse Events Associated with Dropouts, Table 54. Patient # 1075, a 16-year-old girl with systemic onset JRA randomized to receive high-dose celecoxib (8 mg/kg/ day), experienced severe gastritis associated on Day 105. She withdrew from the study on Day 143. Patient # 1211, a 4-year-old girl, experienced severe pruriginous allergic reaction on her hands and feet on Day 1 of receiving high-dose celecoxib (~11.4 mg/kg/day). Patient # 1326, a 13- year-old girl, randomized to high-dose celecoxib (~7.9 mg/kg/day), was hospitalized on Day 57, for a severe flare of her arthritis. Patient # 1343, a 10-year-old girl with systemic onset JRA experienced a severe exacerbation of her JRA on Day 2 of receiving naproxen 15 mg/kg/day. An abnormal urinalysis with urinary protein 2+ and innumerable red blood cells on microscopic examination was reported in this patient.

7.1.3.2 Adverse events associated with dropouts

The common AEs associated with dropouts, study withdrawals, are presented in Table 54. The sponsor and this medical reviewer report 12 patients with AEs causing withdrawal from Study 195. Three of these 12 patients had SAEs associated with their withdrawal from Study 195.

Among the 12 patients with AEs associated with withdrawal, 5 patients received high-dose celecoxib (double-blind phase) and the same in the open-label, 2 patients received low-dose celecoxib (double-blind) and were switched to high-dose celecoxib (open-label phase); 4 patients received naproxen (double-blind phase) and were switched to high-dose celecoxib (open-label); and 1 patient received naproxen in the double-blind phase and withdrew secondary to a severe exacerbation of systemic JRA (not entering the open-label phase).

Among the 3 patients with SAE prompting withdrawal, patient #1075, a 16-year-old female was receiving high-dose celecoxib throughout the double-blind and open-label phase experienced severe gastritis. Her high-dose celecoxib actual dosage was approximately 17 mg/kg/day. Patient # 1211, a 4-year-old female, was receiving high-dose celecoxib actually received approximately 11.4 mg/kg/day and experienced severe pruriginous allergic reaction on her face and hands on Day 1 of study drug. Patient # 1343, a 10-year-old female with systemic JRA experienced a severe exacerbation of her arthritis on Day 2 of receiving naproxen, actual dosage ~15 mg/kg/ day.

There is a possible causal relationship to celecoxib in 9 of 9 patients receiving celecoxib. In the 3 patients receiving naproxen, there is possible causal relationship in each of the 3 cases. Patient # 1057, a 14-year-old-female, experienced upper abdominal pain (Day 15) while receiving naproxen, ~17 mg/kg/day. Patient # 1203, a 16-year-old female, experienced upper abdominal pain as epigastralgia reported on Day 22. Her naproxen dosage was approximately ~12 mg/kg/ day. Patient # 1343, a 10-year-old female, experienced a severe exacerbation of JRA (not systemic features) on Day 2 and later developed proteinuria and hematuria on Day 12 of receiving naproxen, actual dosage ~12 mg/kg/day.

Table 54. Adverse Events Causing Withdrawal from Study 195: Double-Blind or Open-Label

Patient #, Age, Gender	Study Phase DB/OL; Treatment Group, Dosage	Adverse Event, Day of Onset, Concomitant Meds	Comments
# 1029, 7 yr old, F	DB: **Low-dose celecoxib** 6 mg/kg/day (Pt received ~7 mg/kg/day, based on Baseline wt of 27.2 kg)	Dysphagia x 16 days duration. Unable to tolerate taste of study med. Concomitant meds: etanercept, MTX, prednisone, folic acid. Possible study drug rel. (+)	Resolved Day 15
# 1202, 6 yr old, F	DB → OL: DB, **Low-dose celecoxib** 6 mg/kg/day; OL, **High-dose celecoxib** 12 mg/kg/day. DB: (Pt. received ~6.2 mg/kg/day based on Baseline wt of 16 kg) OL: (Pt. received ~ 12.4 mg/kg/day based on	Allergic dermatitis (mild), pruritic, papulo-erythematous lesions on chest, back, and legs on **Day 86.** Withdrawn from study on Day 106. Concomitant meds: MTX, folic acid, prednisone, aluminum hydroxide. Possible study drug rel. (+)	Resolved, Day 108.

Patient #, Age, Gender	Study Phase DB/OL; Treatment Group, Dosage	Adverse Event, Day of Onset, Concomitant Meds	Comments
	Baseline wt. of 16.1 kg.)		
# 1022, 11 yr old, F	DB: **High-dose celecoxib** 12 mg/kg/day (Pt received ~14.2 mg/kg/day, based on wt of 28.2 kg)	Generalized rash, moderate severity, Day 10; celecoxib was discontinued. Concomitant meds: None. Generalized rash, possible study drug rel. (+)	Resolved on Day 14
# 1075, 16 yr old, F Systemic onset JRA	DB → OL: **High-dose celecoxib** 12 mg/kg/day (Pt received ~8.5 mg/kg/day based on Baseline wt. of 47.3 kg.	**Severe gastritis** and mild diarrhea on Day 105 and 106; study medication was discontinued on Day 133. Concomitant meds: prednisone, MTX, folic acid, chloroquine. GI/severe gastritis and diarrhea possibly study drug rel. (+)	Resolved, Day 143.
# 1049, 12 yr old, F	DB: **High-dose celecoxib** 12 mg/kg/day (Pt. received ~11 mg/kg/day, based on Baseline wt. of 35.5 kg)	Innumerable RBCs on microscopic exam, Day 21 considered exacerbation of hematuria; Baseline hematuria 52-70 rbc/hpf. Celecoxib discontinued day 25. Concomitant meds: none except herbal remedies. Possible study drug rel. (+)	Day 42, microscopic hematuria RBCs of 19-33 cells/hpf. Hematuria considered chronic and no further study was reported.
# 1350, 4 yr old, F	DB: **High-dose celecoxib** 12 mg/kg/day (Pt received ~12.7 mg/kg/day based on Baseline wt of 15.7 kg.)	Elevated hepatic enzyme ALT 49 U/L (ULN 34 U/L); On Day 29, ALT ↑ 80 U/L, AST ↑ 53 U/L (ULN 48). Investigator reported on Day 29, study medication stopped on Day 43. Pt was withdrawn from study. Concomitant meds: cyclosporine eye drops for uveitis, calcium, MTX and multivitamin. Possible study drug rel. (+)	ALT and AST within normal limits on Day 43.
# 1211, 4 yr old, F	DB: **High-dose celecoxib** 12 mg/kg/day (Pt received ~11.4 mg/kg/day, based on Baseline wt of 17.5kg)	**Severe pruriginous allergic reaction** on the face and hands on Day 1; study medication was not stopped until Day 5. Possible study drug rel (+);	Resolved Day 7. Sponsor cites subsequent allergy testing to celecoxib by the investigator was negative.
# 1214, 2 yr old, F	DB: **High-dose celecoxib** 12 mg/kg/day	Elevated hepatic enzyme, ALT (40 U/L (ULN 34 U/L) on Day 15; ALT ↑ 185 U/L,	No follow up information provided.

Patient #, Age, Gender	Study Phase DB/OL; Treatment Group, Dosage	Adverse Event, Day of Onset, Concomitant Meds	Comments
	(Pt received ~13.3 mg/kg/day, based on Baseline wt. of 15 kg)	and AST ↑ 94 U/L (ULN 56); reported on Day 36 by Investigator and pt. was withdrawn from study. Concomitant meds: MTX, folic acid, deflazacort. Possible study drug rel. (+)	
# 1325, 11 yr old, F	DB → OL: DB: **naproxen** 15 mg/kg/day (Pt received ~10.4 mg/kg/day, based on Baseline wt of 47.8 kg) OL: **High-dose celecoxib** 12 mg/kg/day	Gastroenteritis, moderate severity on Day 98, withdrawn from study on same day. Concomitant meds: MTX, folic acid, infliximab, calcium, prednisone, cholecalciferol. Possible study drug rel. (+)	Resolved on Day 100.
# 1343, 10 yr old, F, Systemic onset JRA	DB: **naproxen** 15 mg/kg/day (Pt received ~12 mg/kg/day, based on Baseline wt of 32.2 kg)	**Severe exacerbation of JRA** (not systemic features) on Day 2; on Day 13, urinalysis revealed urinary protein of 2+ (innumerable RBCs on microscopic examination). Last dose of study med on Day 12; withdrawn from study on Day 13. Concomitant meds: MTX, folic acid, prednisone, chloroquine, amoxicillin. Possible study drug rel (+).	Urinalysis normal on Day 22
# 1203, 16 yr old, F, Systemic onset JRA	DB: **naproxen** 15 mg/kg/day (Pt received ~12 mg/kg/day based on Baseline wt of 42.9 kg)	Abdominal pain upper/ epigastralgia; nausea and epigastric pain (mild severity) on Day 22; nausea worsened and vomiting started on Day 36; Withdrawn fm study on Day 36. Concomitant meds: MTX, folic acid, prednisone, aluminum hydroxide, calcium carbonate, paracetamol. Possible study drug rel. (+)	Vomiting resolved on Day 38; nausea resolved on Day 42.
# 1057, 14 yr old, F	DB: **naproxen** 15 mg/kg/day (Pt received	Upper abdominal pain, mild on Day 15; severe abdominal pain Day 32; pt. was withdrawn from study. Concomitant meds: MTX,	First episode resolved on Day 20; Second episode resolved in one day (Day 33) with

Patient #, Age, Gender	Study Phase DB/OL; Treatment Group, Dosage	Adverse Event, Day of Onset, Concomitant Meds	Comments
	~ 17 mg/kg/day, based on Baseline wt of 57.7 kg)	folic acid, esomeprazole. Possible study drug rel. (+)	discontinuation of naproxen.
Abbreviations: DB=Double-Blind; OL = Open-Label; rel. = related; pt. = patient; kg = kilogram; ALT= alanine transaminase; AST = asparate transaminase; JR A= juvenile rheumatoid arthritis			

Adult Patients
In the adult cohort of 43 patients with RA in Study 195 (population PK study RR-049), 2 patients experienced a total of 3 adverse events reported as dizziness, diarrhea and urticaria, and withdrew from the population PK study 195 (RR-049). These adverse events are known to be associated with safety profile of celecoxib.

7.1.3.3 Other significant adverse events

All significant adverse events are cited in Section 7.1.2 Other Serious AEs, and in Section 7.1.3 Dropouts and Other Significant AEs.

7.1.4 Other Search Strategies

Safety Analysis in Patients Taking Celecoxib and a Concomitant DMARD, Biologic Response Modifier and or Immunosuppressant

The protocol excluded patients who had begun taking a concomitant DMARD, biologic response modifier and or immunosuppressant medications or had changed the dosing regimen of any of these medications within 12 weeks, except oral gold for 16 weeks and methotrexate for 8 weeks, (or time-frame as designated in the Exclusion Criteria) before receiving the first dose of study medication. See the **Appendix 10.1**, Protocol, Juvenile Rheumatoid Arthritis Exclusion Criteria. Table 55 presents the reported AEs in patients who concurrently received study drug and a biologic response modifier and or an immunosuppressive agent.

There were 30 (39%), 29 (35%) and 28 (34%) patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups who concomitantly received methotrexate. See Table 45.

In the low-dose celecoxib treatment group receiving concomitant methotrexate, there were 113 AEs among 30 patients. The most common AEs were upper abdominal pain, followed by headache NOS. None of these patients had reported elevated hepatic enzymes.

In the high-dose celecoxib treatment group concomitantly receiving methotrexate, there were 41 AEs. The reported AEs were pyrexia (5 events), abdominal pain upper/abdominal pain (5 events), elevated hepatic enzymes (4 events), skin reactions (3 events of which 1 was reported as a SAE in Patient # 1211), diarrhea (3 events), anemia (2 events), 1 flare of asthma reported as a SAE (Patient # 1176), 1 patient with headache reported as a SAE (Patient # 1121), 1 report of myopericarditis reported as a SAE (Patient # 1044), and infections (5 events of nasopharyngitis/ pharyngitis, 2 events of bacteriuria, 1 event each of tonsillitis, and Herpes simplex).

In the naproxen group, there were 129 AEs in patients who received naproxen and concomitant methotrexate. There were 24 experiences of upper abdominal pain upper, 1 of which was severe (Patient # 1057) and 1 event of lower abdominal pain and 2 events of stomach ache, 13 events of headache, 7 events of pyrexia, 6 events of nausea, 5 events of vomiting, 2 events of dizziness, one reported as severe (Patient # 1090), 1 event of increased blood pressure (Patient # 1057) reported as moderate, 1 event as contact dermatitis (poison ivy), 1 event as pain in limb, a separate event as neck pain, both reported as severe (Patient # 1090), 1 event of arthralgia reported as severe (Patient # 1193). Infections were reported as 3 events of tonsillitis, 1 event as sore throat, 1 event as pharyngitis, 4 events of Influenza, and 2 events of Flu.

Table 55. JRA Patients Taking celecoxib and a Baseline Concomitant Biologic Response Modifier or Immunosuppressive Medication, Study 195

Patient #, Age, Gender	**Treatment Group, Concomitant Mediation**	**Adverse Events, Concomitant Meds**
1302, 16 yr old, M	High-dose celecoxib, 12 mg/kg/day Azathioprine	Chest pain in muscles/myalgia, 3 episodes (moderate)
1326, 13 yr old, M	High-dose celecoxib, 12 mg/kg/day; Etanercept	Headache (moderate), Pharyngitis (mild), gastroenteritis (moderate)
1054, 11 yr old, F	Naproxen 15 mg/kg/day; Azathioprine/Infliximab	Joint sprain (mild), eye inflammation (mild), arthralgia aggravated and joint swelling (moderate)
1024, 5 yr old, F	Low-dose celecoxib, 6 mg/kg/day; MTX/Etanercept	Dermatitis (moderate), nasal congestion (mild), wheezing (mild)
1029, 8 yr old, F	Low-dose celecoxib, 6 mg/kg/day; MTX/Etanercept	Dysphagia (severe)
1177, 10 yr old, F	Naproxen 15 mg/kg/day; MTX/Etanercept	Nausea, abdominal pain upper, gastroenteritis NOS, nasopharyngitis (all moderate); worsening JRA (moderate), headaches (severe)
1053, 15 yr old, M	High-dose celecoxib 12 mg/kg/day MTX/ Infliximab	No AEs.
1128, 9 yr old, F	Low-dose celecoxib 6 mg/kg/day; MTX/ Infliximab	Viral infection NOS (moderate)
1325, 12 yr old, F	Naproxen 15 mg/kg/day; MTX/ Infliximab	Allergic reaction to remicade infusion/hypersensitivity (severe); gastroenteritis, vomiting, arthralgia, nasopharyngitis (all moderate)

The safety profile across this small number of patients receiving concomitant MTX and or BRM does not demonstrate a safety signal any larger than in the group not receiving MTX or a BRM.

7.1.5 Common Adverse Events

All patients with JRA, adult patients with RA, and healthy subjects in the pharmacokinetic and CMC studies were included in the safety data review of common AEs. Safety was assessed in each study by clinical laboratory measurements, physical examinations and medical history, vital signs and electrocardiograms (ECGs).

Adult Safety, Pharmacokinetic Studies
There were no deaths or serious adverse events reported in **Study 088, 1162, 1202, or RR 049** from Study 195.

Study 088
There were no adverse events causing withdrawal from Study 088. The adverse events reported in Study 088 are presented in Table 56. One patient reported toothache on the second day of receiving celecoxib. This event is not believed to have a causal relationship to celecoxib.

Table 56. Study 088, Adverse Events, Healthy Adult Subjects

	Celecoxib 50 mg capsule, fasting	**Celecoxib 50 mg capsule high-fat breakfast**	**Celecoxib 100 mg capsule, fasting**	**Celecoxib 100 mg capsule high-fat breakfast**
Extent of Exposure N = Subjects	24	24	24	24
Discontinuations/withdrawals	0	0	0	0
Adverse Event				
Toothache, mild*	0	0	1	0
* Experienced a toothache one day after receiving study drug.				

There were no statistically significant changes, with respect to the normal range, noted from Baseline to post-treatment, for any of the laboratory parameters. There were statistically significant changes from Baseline in the mean laboratory values for albumin, partial thrombo-plastin time (PTT), hematocrit, BUN, sodium and urine pH. This medical reviewer concurs with the sponsor, that none of these changes exceeded the normal range. No dose-related trends in adverse events can be drawn from these results.

Study 1162
Headaches occurred in 3 of the 4 treatment groups. Hemorrhage (mild subcutaneous hemorrhage of the left lower eyelid) was reported in 1 patient who received celecoxib 200 mg oral suspension, and syncope (moderate) was reported in 1 person who received 400 mg celecoxib capsule. Twitching (mild) was reported in the 200 mg and 400 mg oral suspension treatment group. Dizziness (moderate) was reported only in the 200 mg celecoxib capsule group. There was one accidental injury (moderate) reported in the 200 mg oral suspension treatment group. See Table 57. Twitching is not reported in the adult adverse event profile of celecoxib.

Table 57. Study 1162, Adverse Events, Adult Healthy Subjects

	Treatment Group			
Adverse Event by Body System	**Celecoxib 200 mg capsule N =19**	**Celecoxib 400 mg capsule N = 20**	**Celecoxib 200 mg suspension, 20 mg/mL N = 19**	**Celecoxib 400 mg suspension, 20 mg/mL N = 19**
Digestive System				
Diarrhea	0	0	0	1
Dry Mouth	0	0	0	1
Vomiting	0	0	0	1
Nausea	1	0	0	0
Body as a Whole				
Headache	1	1	0	1
Abdominal pain	1	0	0	0
Accidental Injury	0	0	1	0
Infection	0	1	0	0
Nervous System				
Twitching	0	0	1	1
Dizziness	1	0	0	0
Skin and Appendages				
Contact dermatitis	0	0	0	1
Cardiovascular System				
Hemorrhage	0	0	1	0
Syncope	0	1	0	0
Respiratory system				
Rhinitis	1	0	0	0
Total AEs	**5**	**3**	**3**	**6**

The clinical laboratory results from Study 1162 did not demonstrate any clinically meaningful findings.

Study 1202

There were 9 AEs reported from 7 subjects. Headaches were reported in both treatment groups, and 1 report of "flushing" with the 100 mg capsule sprinkled onto applesauce group. There were no clinically important physical examination findings, vital signs, or ECG findings in Study 1202. See Table 58.

Table 58. Study 1202, Adverse Events, Healthy Adults

	Celecoxib 100 mg capsule (Intact)	**Celecoxib 100 mg capsule (sprinkled onto applesauce)**
Total # Subjects	**24**	**24**
Total # AEs	**5**	**4**
Gastrointestinal disorders		
Abdominal pain	1	0
Diarrhea	1	0
General disorders and administration site conditions		
Hunger	1	0
Infections and infestations		
Upper respiratory tract infection	0	1

viral infection	0	1
Nervous system disorders		
Headache	1	1
Respiratory, thoracic and mediastinal disorders		
Hiccups	1	0
Vascular disorders		
Flushing	0	1
*Includes data up to 28 days after the last dose of study drug. Systemic Organ Class and MedDRA v8.1 preferred term)		

Study 195
Pediatric Patients

There were 804 AEs reported across all three treatment groups for the total duration of 24 weeks. The most common AEs reported across the three treatment groups were GI events (28%), infections and infestations (15%), nervous system (11%), musculoskeletal, connective tissue and bone disorders (10%), respiratory, thoracic and mediastinal disorders (9%), general disorders and administration site conditions (8%), skin and subcutaneous tissue disorders (5%), investigations (3%), and eye disorders, injury and poisoning, blood and lymphatic system disorders, each as (2%). See Table 59.

Respiratory, thoracic and mediastinal, eye disorders, and metabolic and nutrition disorders were the 3 body systems where the study drug, low-dose and or high-dose celecoxib, demonstrated more AEs than were reported in the naproxen, active comparator treatment group across the total 24 week duration of Study 195. In the respiratory body system, there were 20 AEs (low-dose celecoxib), 32 AEs (high-dose celecoxib) and 17 AEs (naproxen); in the eye disorders body system, there were 8 AEs (low-dose celecoxib), 5 AEs (high-dose celecoxib) and 4 AEs (naproxen); and in the metabolic and nutrition disorders, there were 3 AEs (low-dose celecoxib), 2 AEs (high-dose celecoxib) and 1 AE (naproxen) in the treatment groups.

Overall, there was comparable incidence of GI experiences, 87 AEs (low-dose celecoxib), 54 AEs (high-dose celecoxib) and 87 AEs (naproxen) treatment groups. Overall, naproxen demonstrated more AEs in the following body systems as compared to low-dose celecoxib or high-dose celecoxib: infections and infestations (44 AEs, naproxen, compared to 41 AEs low-dose celecoxib and 39 AEs, high-dose celecoxib); nervous system disorders (50 AEs naproxen, compared to 25 AEs, low-doe celecoxib, and 17 AEs, high-dose celecoxib); musculoskeletal, connective tissue and bone disorders (37 AEs, naproxen, compared to 25 AEs, low-doe celecoxib, and 18 AEs, high-dose celecoxib); general disorders (26 AEs, naproxen, compared to 21 AEs, low-dose celecoxib, and 19 AEs, high-dose celecoxib); skin and subcutaneous disorders (20 AEs, naproxen, 14 AEs, low-dose celecoxib, and 8 AEs, high-dose celecoxib); reproductive system and breasts disorders (3 AEs, naproxen, compared to 2 AEs, low-dose celecoxib, and 1 AE, high-dose celecoxib); renal and urinary disorders (2 AES, naproxen, compared to 1 AE, low-dose celecoxib and 0 AE, high-dose celecoxib); and vascular disorders (1 AE, naproxen, compared to 0 in the low-dose and 0 in the high-dose celecoxib groups).

The AES in the naproxen group were either less than or equal to one of the two celecoxib study groups in the following body systems: investigations (10 AEs, naproxen, compared to 4 AEs, low-dose celecoxib only; there were 11 AEs, high-dose celecoxib demonstrated 11 AEs); and, blood and lymphatic system disorders (6 AEs, naproxen, compared to 1 AE, low-dose celecoxib; there were also 6 AEs, high-dose celecoxib).

Overall, the incidence of AEs were comparable, with a small increase in the high-dose celecoxib group, compared to the low-dose celecoxib and the naproxen group in the following body systems: Immune system (2 AEs in naproxen, compared to 2 AEs, low-dose celecoxib and 4 AEs, high-dose celecoxib); psychiatric disorders (1 AE in naproxen, compared to 1 AE, low-dose celecoxib, and 2 AEs, high-dose celecoxib). There was equal incidence of AEs across the three treatment groups (5 AEs) in the body system, injury and poisoning. See Table 59.

Table 59. Incidence of All Adverse Events in Patients with JRA: 24 Weeks, Study 195

Body System	Celecoxib 6 mg/kg/day N-=AEs	Celecoxib 12 mg/kg/day N= AEs	Naproxen 15 mg/kg/day N=AEs	Total # AEs (%)
Gastrointestinal Disorders	87	54	87	228 (28%)
Infections and Infestations	41	39	44	124 (15%)
Nervous system Disorders	25	17	50	92 11%)
Musculoskeletal, Connective Tissue and Bone Disorders	25	18	37	80 (10%)
Respiratory, Thoracic and Mediastinal Disorders	20	32	17	69 (9%)
General Disorders and Administration site Conditions	21	19	26	66 (8%)
Skin and subcutaneous Tissue Disorders	14	8	20	42 (5%)
Investigations	4	11	10	25 (3%)
Eye Disorders	8	5	4	17 (2%)
Injury and Poisoning	5	5	5	15 (2%)
Blood and Lymphatic System Disorders	1	6	6	13 (2%)
Reproductive System and Breast Disorders	2	1	3	6 (1%)
Immune system Disorders	2	4	2	8 (1%)
Metabolism and	3	2	1	6 1%)

Nutrition Disorders				
Psychiatric Disorders	1	2	1	4 (0.50%)
Ear and Labyrinth Disorders	2	1	0	3 (0%)
Renal and Urinary Disorders	1	0	2	3 (0%)
Cardiac Disorders	0	1	0	1 (0%)
Vascular Disorders	0	0	1	1 (0%)
Total AEs	**262 (33%)**	**225 (28%)**	**317 (39%)**	**804**

The AEs for all juvenile patients in the double-blind phase, by treatment group, are compared to the adverse events in the open-label phase, reported by the previous treatment group of the study patient. See Table 60, low-dose celecoxib in the double-blind phase transitioned to high-dose celecoxib in the open-label phase; Table 61, high-dose celecoxib in the double-blind phase, remaining the same in the open-label phase; and Table 62, naproxen 15 mg/kg/day in the double-blind phase, transitioned to high-dose celecoxib in the open-label phase.

Gastrointestinal AEs were the most common adverse event across the three treatment groups, 66 events (35%), 33 events (22%) and 70 events (29%), low-dose celecoxib, high-dose celecoxib and naproxen 7.5 mg/kg BID, respectively, in the double-blind phase. The GI events were specifically reported were abdominal pain upper, abdominal pain, nausea, diarrhea, vomiting, abdominal pain lower, dysphagia, gastrointestinal hemorrhage NOS, gastritis, flatulence, esophageal pain, rectal bleeding, mouth ulceration, stomatitis, constipation, and gastrointestinal pain.

I**nfections and infestations** were the second most commonly reported body system with AEs reported in the double-blind phase, 26 events (14%), 24 events (16%) and 27 events (11%) in the low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, in the double-blind phase. In the naproxen treatment group, double-blind phase, infections and infestations were the third most commonly reported adverse event. The AEs were reported as nasopharyngitis, herpes zoster, pharyngitis streptococcal, upper respiratory tract infection, Influenza, tonsillitis, lice infestation, urinary tract infection, molluscum contagiosum, gastroenteritis viral, Herpes simplex, ear infection, viral infection, tinea versicolor, lower respiratory tract infection, croup infectious, bronchitis acute NOS, Fifth's disease, and hepatitis cytomegalovirus.

In the naproxen treatment group, double-blind phase, the second most commonly reported adverse events were in the **nervous system**, 42 events (17%). In the low-dose celecoxib and the high-dose celecoxib treatment groups, the AEs were 18 (10%) and 11 (7%), respectively, in the double-blind phase. The reported events were headaches, headache NOS, disturbance in attention NEC, dizziness (exc vertigo), hypoaesthesia, and migraine aggravated.

Respiratory, thoracic and mediastinal disorders were reported as 12 events (6%), 25 events (17%) and 17 events (7%) in low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, in the double-blind phase. The incidence was more than double in the high-dose celecoxib treatment group as compared to the low-dose celecoxib or the naproxen treatment group. The AES in this body system were cough, rhinorrhea, nasal congestion, wheezing, dyspnea exacerbated, epistaxis and snoring.

The incidence of **musculoskeletal, connective tissue and bone disorder** AEs was 17 (9%), 10 (7%) and 24 (10%) in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, in the double-blind phase. Flare of JRA, joint swelling, joint stiffness, arthralgia aggravated, pain in limb, synovial cyst, back pain, neck pain and tendon disorder NOS were the AEs reported in this body system.

General disorders and administrative site conditions were reported in 17 (9%), 13 (9%) and 21 (9%) of patients in the double-blind phase. Pyrexia, fever, injection site hemorrhage, groin pain, chest pain, fatigue, weakness, drug intolerance. Pyrexia occurred most frequently and was reported across all three treatment groups, in the double-blind phase.

Skin and subcutaneous tissue disorders were reported in 11 (6%), 6 (4%) and 15 (6%) of patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, in the double-blind phase. The AEs were rash, subcutaneous nodules, allergic rash, dermatitis allergic, contact dermatitis, pruritus generalized, and pustulosys. See adverse events causing withdrawal, patient # 1022 (celecoxib 6 mg/kg BID), patient # 1211 (celecoxib 6 mg/kg BID) and patient # 1202 (celecoxib 3 mg/kg BID entered in the celecoxib 6 mg/kg BID treatment group) for details of skin events.

Eye disorders as a body system were reported as 5 (3%), 4 (3%) and 4 (2%) in the low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, double-blind phase. Mild uveitis was reported as 4 adverse events, 2 episodes (right eye and left eye) in patient # 1148, low-dose celecoxib treatment group; patient # 1213, low-dose celecoxib treatment group; and patient # 1217, high-dose celecoxib treatment group, in the double-blind phase. Blurred vision was reported as 2 episodes in patient # 1129, low-dose celecoxib treatment group, in the double-blind phase.

Injury and poisoning events were reported as 3 (2%), 5 (3%), and 4 (2%) in the low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, in the double-blind phase. Each of these events except 1 involved trauma at play. There was one intentional overdose reported in patient # 1088.

Table 60 Adverse Events, Celecoxib 6 mg/kg/day, Reported by Double-Blind and Previous Treatment in the Open-Label Phase

System Organ Class	Double-Blind Phase: Low-dose celecoxib 6 mg/kg/day	Open-Label Phase: Previous Exposure to Low-dose celecoxib 6 mg/kg/day→ OL, High-dose celecoxib 12 mg/kg/day
Gastrointestinal Disorders	66 (35%)	21 (28%)
Infections and Infestations	26 (14%)	15 (20%)
Respiratory, thoracic, mediastinal disorders	12 (6%)	8 (11%)
General disorders and administrative site conditions	17 (9%)	4 (5%)
Nervous system	18 (10%)	7 (9%)
Musculoskeletal, connective tissue, and bone disorders	17 (9%)	8 (11%)
Investigations	2 (1%)	2 (3%)
Injury and poisoning	3 (2%)	2 (3%)
Immune system	1 (1%)	1 (1%)
Blood and lymphatic system disorders	1 (1%)	0 (0%)
Skin and subcutaneous tissue disorders	11 (6%)	3 (4%)
Eye disorders	5 (3%)	3 (4%)
Psychiatric disorders	0 (0%)	1 (1%)
Ear and labyrinth disorders	1 (1%)	1 (1%)
Cardiac disorders	0 (0%)	0 (0%)
Metabolism and nutrition disorders	3 (2%)	0 (0%)
Reproductive system and breast disorders	2 (1%)	0 (0%)
Total AEs	**186**	**76**

Table 61. Adverse Events, Celecoxib 12 mg/kg/day, Reported by Double-Blind and Open-Label Phase

System Organ Class	Double-Blind Phase: Celecoxib 12 mg/kg/day	→ Open-Label Phase: Celecoxib 12 m/kg/day
Gastrointestinal Disorders	33 (22%)	21 (28%)
Infections and Infestations	24 (16%)	15 (20%)
Respiratory, thoracic, mediastinal disorders	25 (17%)	7 (9%)
General disorders and administrative site conditions	13 (9%)	6 (8%)
Nervous system	11 (7%)	6 (8%)
Musculoskeletal, connective tissue, and bone disorders	10 (7%)	8 (11%)
Investigations	10 (7%)	1 (1%)

Injury and poisoning	5 (3%)	0 (0%)
Immune system	3 (2%)	1 (1%)
Blood and lymphatic system disorders	2 (1%)	4 (5%)
Skin and subcutaneous tissue disorders	6 (4%)	2 (3%)
Eye disorders	4 (3%)	1 (1%)
Psychiatric disorders	2 (1%)	0 (0%)
Ear and labyrinth disorders	1 (1%)	0 (0%)
Cardiac disorders	0 (0%)	2 (3%)
Metabolism and nutrition disorders	0 (0%)	2 (3%)
Reproductive system and breast disorders	1 (1%)	0 (0%)
Total AEs	**150 events**	**75 events**

Table 62. Adverse Events, Naproxen 15 mg/kg/day, Reported by Double-Blind and Previous Treatment in the Open-Label Phase

System Organ Class	**Double-Blind Phase: Naproxen 15 mg/kg/day**	**Open-Label Phase: Previous Exposure to Naproxen 15 mg/kg/day → OL, High-dose celecoxib 12 mg/kg/day**
Gastrointestinal Disorders	70 (29%)	17 (22%)
Infections and Infestations	27 (11%)	17 (22%)
Respiratory, thoracic, mediastinal disorders	17 (7%)	0 (0%)
General disorders and administrative site conditions	21 (9%)	5 (7%)
Nervous system	42 (17%)	8 (11%)
Musculoskeletal, connective tissue, and bone disorders	24 (10%)	13 (17%)
Investigations	7 (3%)	3 (4%)
Injury and poisoning	4 (2%)	1 (1%)
Immune system	1 (0%)	1 (1%)
Blood and lymphatic system disorders	2 (1%)	4 (5%)
Skin and subcutaneous tissue disorders	15 (6%)	5 (7%)
Eye disorders	4 (2%)	0 (0%)
Psychiatric disorders	1 (0%)	0 (0%)
Ear and labyrinth disorders	0 (0%)	0 (0%)
Cardiac disorders	0 (0%)	0 (0%)
Metabolism and nutrition disorders	1 (0%)	1 (0%)
Reproductive system and breast disorders	2 (1%)	1 (1%)
Vascular	1 (1%)	0 (0%)
Total AEs	**241**	**76**

Adverse Events in Younger and Smaller Weight Patients
There is a positive trend toward increased adverse events in the younger and smaller weight patients who received high-dose celecoxib compared to low-dose celecoxib. In patients **< 7 years** of age, there were **60 (23%), 85 (37%) and 66 (21%) of all AEs in Study 195 reported in 13, 22 and 14 patients** in **low-dose celecoxib, high-dose celecoxib and naproxen groups,** respectively. **There were almost double the incidence in the high-dose celecoxib group compared to the low-dose and naproxen groups.** In the low-dose celecoxib group, patient weight ranged from 12.2 kg to 24.5 kg; in the high-dose celecoxib group, patient weight ranged from 11.4 kg to 37.5 kg; and in the naproxen group, patient weight ranged from 13.2 kg to 30.8 kg.

A. Low-Dose Celecoxib AEs
In the low-dose celecoxib group, the most common AES were:

- **Infection:** nasopharyngitis, pharyngitis, ear infection, influenza and acute bronchitis (6 patients who were 12.2 kg to 24.5 kg)
- **GI events**: abdominal pain upper, diarrhea and vomiting (3 patients who were 3.6, 4.4 and 4.8 years of age with body weight 15.1 kg, 18.7 kg and 16.3 kg, respectively);
- **Nervous System:** Headache;
- A**llergic dermatitis reactions (**3 patients who were 2, 3.5 and 6.2 years of age with 12.2 kg, 16.5 kg and 15 kg body weight, respectively)

Less common AES in the low-dose group were: pyrexia, elevated CPK (moderate), uveitis, corneal opacity, drug intolerance.

B. High-Dose Celecoxib AEs
In the high-dose celecoxib group, the most common AES were:

- **Infection:** Pharyngitis, rhinorrhea, otitis media and urinary tract infection (**severe**);
- **GI:** Abdominal pain/upper, vomiting and diarrhea;
- **Skin:** Allergic dermatitis/hypersensitivity reaction (**severe** reaction), dermatitis;
- **General Systems:** Pyrexia, nervousness, anxiety;
- **Musculoskeletal:** arthralgias, joint swelling, pain in limb, groin pain;
- **Nervous System:** Headache, anxiety;
- **Laboratory tests:** elevation of hepatic enzymes (moderate, in one pt 2.9 years of age, 15 kg), increased blood glucose (one 6.7 year old, 18.2 kg);

Less common AEs in the high-dose group were: asthma-flare (**severe**, in a 6.7 year old, 20 kg), wheezing (4.6 year old, 37.5 kg); uveitis.

C. Naproxen AEs
In the naproxen group, the most common AEs were:

- **GI:** abdominal pain/upper, gastrointestinal pain, diarrhea, vomiting;
- **Infection:** Pharyngitis, tonsillitis, streptococcal tonsillitis (severe) rhinitis, Fifth's disease;
- **General:** Pyrexia, irritability.
- **Nervous system:** Headache, irritability.

Less common AEs in the naproxen group were: Elevated blood uric acid (5.3 year old, 23kg)

7.1.5.1 Eliciting adverse events data in the development program

The clinical investigator's obtained and recorded on the CRF all observed or volunteered adverse events, the severity (mild, moderate, or severe) of the events and the investigator's opinion of the relationship to the study treatment. Adverse events included adverse drug reactions, illness with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator recorded as adverse events any clinically significant changes in physical examination finding and abnormal objective test findings (e.g., electrocardiogram [ECG], x-ray, clinical laboratory). [Note: ECGs were not routinely performed in Study 195.] A serious adverse event or serious adverse drug reaction was any untoward medical occurrence at any dose that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, flare of systemic features or resulted in congenital anomaly/birth defect. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor applied appropriate MedDRA and preferred terms to the reporting of adverse events.

7.1.5.3 Incidence of common adverse events

See Section 7.1.5 Common Adverse Events. The common adverse events are consistent with those reported from use of NSAIDs. There is absence of common adverse events for experiences of hypertension, renal involvement and cardiovascular events, specifically, thromboembolic events. The protocol monitoring of blood pressure change in this pediatric population may account for the absence of hypertension as a reported adverse event. There was one patient (naproxen group) who experienced hypertension.

7.1.5.4 Common adverse event tables

See Section 7.1.5 Common Adverse Events for the Tables demonstrating the safety analyses of common AEs.

7.1.5.5 Identifying common and drug-related adverse events

See Section 7.1.5 Common Adverse Events. This reviewer designated those patient experiences where study drug causality could be concluded or not excluded.

7.1.5.6 Additional analyses and explorations

Race:
In view of the incidence of JRA in the pediatric population and the small numbers in this study, the racial demographics are representative of the disease incidence and there was no disproportionate incidence by racial group in the safety database.

Gender:
In view of the small numbers and the relative balance across the treatment groups, there was no clinically meaningful difference in the incidence of adverse events beyond the finding that there are more girls than boys with JRA and similarly, there were more girls than boys enrolled in Study 195. See Section 6.1.4 Efficacy Findings, Table 4, Demographics for Study 195.

Concomitant Medication:
Celecoxib and a Concomitant DMARD, Biologic Response Modifier and or Immunosuppressant
See Section 7.1.4 Other Search Strategies

JRA Patients who Received Celecoxib as 100 mg to 200 mg Total Daily Dose [Proposed Dosage]
See Section 6.1 Efficacy, Exploratory Analyses.

7.1.6 Less Common Adverse Events

Disseminated Intravascular Coagulation
There were 2 unlabeled adverse event categories reported in this supplement. See Section 7.1.2, Serious Adverse Events for explanation of the one unlabeled SAE of disseminated intravascular coagulation (DIC) that is reported in patient # 1044, a 15-year-old boy with systemic JRA (high-dose celecoxib group) who experienced myopericarditis and laboratory evidence of DIC with the high extreme criteria for PT (> 15.9 sec). The laboratory findings in DIC are typically prolonged partial thromboplastin time (PTT), prolonged prothrombin time (PT), prolonged thrombin time (PTT), lower platelets, positive fibrin split products (FSPs), lower fibrinogen and lower Factor VIII. There appears to be a possible causal relationship between the study drug and this SAE. In the sub-group population of systemic onset JRA, elevation of PT, PTT, APTT could be the early stage of DIC. The occurrence of abnormal coagulation laboratory tests/DIC in patients with systemic JRA is documented in the pediatric literature (macrophage activation syndrome) and is a reported risk with administration of NSAIDs. **The current celecoxib label does not include the event of DIC.**

There were other patients in Study 195 with abnormal coagulation laboratory results, most notably a prolonged activated partial thromboplastin time (APTT).

- **Low-dose celecoxib group:** 6 and 7 patients met the extreme high criteria for APTT (> 41.0 sec) and maximum value, respectively, in the double-blind phase.
- **High-dose celecoxib group:** 5 and 7 patients met the extreme high criteria for APTT and the maximum value, respectively.
- **Naproxen group:** 1 and 5 patients met the high extreme criteria for APTT and the maximum value, respectively.

Twitching
There was 1 adult patient who experienced twitching with the administration of celecoxib 200 mg/day and also with celecoxib 400 mg/day. The metabolic profile was reported as normal in the individual. It was concluded that celecoxib could have a causal relationship to these two events of twitching. **Twitching is an unlabeled event in the current celecoxib label.**

Flare of Systemic JRA
At randomization in Study 195, there were 4 (5%), 10 (12%) and 8 (9%) patients who had systemic onset JRA, but with currently inactive systemic features, in low-dose celecoxib, high-dose celecoxib and the naproxen treatment groups, respectively. **Overall, there were 5 patients (23%) with systemic onset JRA who experienced SAEs or severe adverse events, 1 of 4 (25%), 2 of 10 (20%), and 2 of 8 (25%) patients, in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively.** Systemic JRA appears to be at greater risk for serious adverse events than is pauciarticular and polyarticular JRA in the setting of non-selective NSAIDS/COX-2 selective inhibitors.

7.1.7 Laboratory Findings

Overall, the mean hematology changes in the double-blind phase of Study 195 were not considered to be meaningful in the JRA population except in the naproxen 15 mg/kg/day treatment group in which a mean decrease of 4.4 g/L in hemoglobin compared to a mean decrease of 2.1 g/L in the low-dose celecoxib treatment group and a mean decrease of 1.2 g/L in the high-dose celecoxib treatment group was noted. Hematology values which met the extreme low criteria established by the sponsor, the neutrophil count met the low extreme criteria (below 1000 x 10^6/L) in the high-dose celecoxib treatment group for 1 patient at minimum value. In the naproxen treatment group, hemoglobin met the low extreme criteria (below 80 or 30 g/L decrease from Baseline) in 1 subject at the final double-blind visit and 1 subject at minimum value, and lymphocyte count met the low extreme criteria (below 500 x 10^6/L) in 1 subject at minimum value.

In the low-dose celecoxib group, 3 patients demonstrated high extreme lymphocyte counts above 5000 x 10^6/L, and 2 patients demonstrated high basophile counts (above 150 x 10^6/L) and 5 patients demonstrated high eosinophil counts (above 300 x 10^6/L) in the double-blind phase. In the high-dose celecoxib treatment group, hematology values reached the high extreme criteria as an eosinophil count (above 300 x 10^6/L) for 3 and 7 patients in the double-blind phase by Week 12. Mild leucopenia was reported in patient # 1097, naproxen treatment group, double-blind phase. Mild thrombocytopenia was reported in one patient, # 1097, naproxen treatment group.

During the open-label phase, patients who were switched from double-blind naproxen treatment group to high-dose celecoxib experienced a mean increase in hemoglobin of 2.9 g/L. Otherwise, overall mean changes in hematology laboratory values were small and unremarkable.

Laboratory AEs reported as investigations were reported as 2 (1%), 10 (7%) and 7 (3%) in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively, in the double-blind phase. Hematuria exacerbation was reported as severe in patient # 1049 who was treated with high-dose celecoxib. See Table 54.

Overall the mean changes from Baseline in chemistry laboratory tests in the double-blind phase were small and not considered clinically meaningful except for hepatic enzymes, uric acid and creatinine phosphokinase. The most common adverse event reported as laboratory AEs were elevated liver enzymes: patient # 1003, celecoxib 3 mg/kg BID treatment group, moderate elevation of LFTs; patient # 1241, celecoxib 6 mg/kg BID treatment group, 2 events of mild elevation of LFTs, and patient # 1214, celecoxib 6 mg/kg BID treatment group, moderate elevation of transaminase enzymes, and patient # 1350, celecoxib 6 mg/kg BID treatment group, mild severity. There were no reports of elevated hepatic enzymes as AEs in patients taking the active comparator naproxen in the AE reports.

There were no panic values in BUN or electrolytes. The urinalyses with maximum values were small and reported in all three treatment groups. Mild proteinuria was reported in two patients, # 1265 and # 1343, both in the naproxen treatment group, double-blind phase.

Elevated blood uric acid was reported in patient # 1006, naproxen treatment group, as moderate severity, and reported in patient # 1083, celecoxib 6 mg/kg BID treatment group, as mild hypericemia.

Blood creatine phosphokinase elevation was reported in 4 patients: severe in patient # 1175, celecoxib 3 mg/kg BID treatment group, double-blind; patient # 1213, celecoxib 3 mg/kg BID treatment group, as high panic value of creatine phosphokinase (moderate severity) and in patient # 1295, naproxen treatment group, 2 events of mild elevation of creatinine phosphokinase.

Metabolic and nutrition adverse events were reported as 3 (2%), 0 (0%) and 1 (0%) adverse events in the low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, in the double-blind phase. Mild hyperuricemia was reported as an AE in one patient (# 1083), high-dose celecoxib. Mild elevation blood glucose was reported in patient # 1009, low-dose celecoxib, double-blind phase. Mild hypoglycemia was reported in one patient # 1379, naproxen treatment group, in the double-blind phase.

The overall mean changes in coagulation laboratory tests were reported across all three treatment groups. See Section 7.1.6 Less Common Adverse Events.

In the analysis of systolic blood pressure (SBP) during the double-blind phase of the study with treatment group as a factor and baseline value, gender, age, and height as covariates, the least squares mean changes in SBP were 0.91, 0.76, and 1.60 mm Hg for the low-dose celecoxib, the high-dose celecoxib and the naproxen treatment group, respectively. In analysis of the extreme values by week-12, there was a small trend toward the active comparator compared to the low-dose and high-dose celecoxib, for slight increase in systolic blood pressure.

In the analysis of diastolic blood pressure (DBP) with treatment group as a factor and baseline value, gender, age, and height as covariates, least squares mean changes in DBP were -0.80, -0.49, and -1.25 mm Hg for the low-dose celecoxib, the high-dose celecoxib and the naproxen treatment group, respectively. The data suggests a small trend (measured as 15 % from Baseline, week-12 and week-24) for increase in diastolic BP more than in systolic BP. The statistic reviewer analyzed the raw data for blood pressure, as reported, and was not able detect a

difference. Increased blood pressure (moderate severity) as an adverse event was reported in only one patient (# 1057) in the naproxen treatment group.
The extreme vital signs were reported as a 15% increase from Baseline at Week-12 and at Week-24. A single maximum value was reported. An extreme threshold of 15% increase from Baseline, based on a single BP assessment, may to be too high to detect trends in blood pressure changes in pediatric patients receiving non-selective NSAIDs/COX-2 selective inhibitors. The **blood pressure data may not be sufficient in Study 195 to make an adequate assessment of potential blood pressure changes in these pediatric patients.** The sponsor acknowledged during a meeting with the Division on October 18, 2006 and noted during the Arthritis Advisory Committee meeting on November 29, 2006, that the blood pressure monitoring in Study 195 was monitored with an adult threshold for change in systolic and/or diastolic blood pressure (e.g., higher than 15% change) than are recommended for monitoring systolic and/or diastolic blood pressure change in pediatric patients. This may be the possible rationale for the potential under reporting of blood pressure elevation in Study 195. Elevation of systolic blood pressure with the administration of non-selective NSAID/COX-2 selective inhibitors is commonly dose-dependent.

7.1.7.1 Overview of laboratory testing in the development program

Except for the procedure of assessing systolic and diastolic blood pressure in pediatric patients participating in Study 195, the overall laboratory testing program was adequate in this pediatric supplement. See comments about blood pressure thresholds and measurement in Section 7.1.7 Laboratory Findings.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This section is not applicable to this supplement review.

7.1.7.3 Standard analyses and explorations of laboratory data

Descriptive statistics were applied to analyze laboratory results. See Section 7.1.7 Laboratory Findings.

7.1.7.3.1 Analyses focused on measures of central tendency

No additional analyses of central tendency were performed. See the Statistic review by Katherine Meaker, PhD.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

See comments in Section 7.1.7 Laboratory Findings. As the patient numbers are small, no additional analyses were performed.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See comments in Section 7.1.7 Laboratory Findings.

7.1.7.4 Additional analyses and explorations

There were no additional analyses in this pediatric supplement.

7.1.7.5 Special assessments

See Section 7.1 Safety Review, Common Adverse Events.

7.1.8 Vital Signs

In Study 195, there is only one report of increased blood pressure as an adverse event (moderate severity). This event was reported in patient # 1057, a 14-year-old girl with JRA who was randomized to the naproxen treatment group (~17 mg/kg/day) and was concomitantly taking methotrexate, folic acid and esomeprazole. She was reported to have high blood pressure (moderate) onset on Day 6 for a total duration of 9 days. See Section 7.1.3.2 Adverse Events Associated with Dropouts and Table SB5, and see reviewer comments in Section 7.1.7 Laboratory Findings.

7.1.8.1 Overview of vital signs testing in the development program

Vital sign testing in Study 195 was adequate except for the procedures to measure and assess systolic and diastolic blood pressure in pediatric patients. See reviewer comments in Section 7.1.7 Laboratory Findings.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

There were no additional drug control comparison studies in this Supplement.

7.1.8.3 Standard analyses and explorations of vital signs data

See Section 7.1.7 Laboratory Findings.

7.1.8.3.1 Analyses focused on measures of central tendencies

See Section 7.1.7 Laboratory Findings.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

See Section 7.1.7 Laboratory Findings

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

See Section 7.1.7 Laboratory Findings

7.1.8.4 Additional analyses and explorations

There are no additional analyses and explorations in Study 195.

7.1.9 Electrocardiograms (ECGs)

In Study 195, there were no electrocardiogram assessments included in the protocol for these pediatric patients. As the safety concerns for serious adverse cardiovascular events with the administration of non-selective NSAIDs/COX-2 selective inhibitors has significantly increased since Protocol 195 was submitted to the Agency, ECG assessment would need to be considered in any subsequent pediatric clinical trials with non-selective NSAIDs/COX-2 selective inhibitors.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

This section is not applicable to this pediatric supplement.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This section does not apply to this pediatric supplement.

7.1.9.3 Standard analyses and explorations of ECG data

ECGs were not performed in Study 195. See reviewer comments in Section 7.1.9 Electrocardiograms

7.1.9.3.1 Analyses focused on measures of central tendency

See Section 7.1.9.3 above.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See Section 7.1.9.3 above.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See Section 7.1.9 ECGs

7.1.9.4 Additional analyses and explorations

This section is not applicable to this pediatric supplement.

7.1.10 Immunogenicity

Immunogenicity was reported with the original NDA 20-998 submission.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were reviewed in the original celecoxib NDA 20-998 application.

7.1.12 Special Safety Studies

There were no special safety studies beyond the Phase 3 pivotal Study 195 submitted with this Supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Abuse potential of celecoxib is not discussed in the current label.

7.1.14 Human Reproduction and Pregnancy Data

See the current label for celecoxib, Section: Pregnancy, and the Section: Carcinogenesis, mutagenesis, impairment of fertility. See the Pharmacology/Toxicology review by Gary Bond, PhD. The eligibility criteria in Study 195 are appropriate for the protection of child-bearing age females. See Appendix 10.1, Protocol 195.

7.1.15 Assessment of Effect on Growth

Growth and Development
As noted by the sponsor and this reviewer, growth disturbances are characteristic of JRA in all sub-type by course. Linear growth is usually retarded during periods of active disease. Therefore, growth and development were assessed by measuring height and weight at the Baseline and Weeks 12 (or Early Termination in the double-blind phase) and 24 (or Early Termination in the open-label phase) visits. Weight was measured in kilograms (kg) and height in centimeters (cm). There were no patients entering Study 195 who were reported to be experiencing developmental delays. There were developmental delays or loss of developmental milestones reported as adverse events during Study 195.

Weight
There were no statistically significant differences reported among treatment groups in the mean changes in weight or in the extreme weight values with combined gender and age.

Height
There were no statistically significant differences reported among treatment groups in the mean changes in height

Uveitis and Other Eye Disorders
At Baseline, the sponsor reported 3 (4%), 3 (4%) and 3 (4%) JRA patients in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups with abnormal slit lamp examination at Baseline. By 12-week visit, there were 1 (2%), 2 (3%) and 3 (5%) JRA patients in the low-dose celecoxib, high-dose celecoxib, and naproxen treatment groups, respectively, with abnormal slit lamp examinations.

In the low-dose celecoxib treatment group, 1 patient developed uveitis NOS and 1 patient developed blurred vision. In the high-dose celecoxib treatment group, 1 patient developed eye disorder NOS and 1 patient developed uveitis. In the naproxen treatment group 1 patient

developed anterior chamber disorder NOS and 1 patient developed eye inflammation. The eye disorders do not appear to be casually related to the study medications.

In the open-label phase, high-dose celecoxib treatment group, 1 patient (0.5%) developed corneal opacity and 1 patient (0.5%) developed uveitis.

7.1.16 Overdose Experience

There was one patient with JRA in Study 195 who is reported to have taken an intentional overdose of celecoxib and erythromycin. The experience of patient (# 1088) is presented in Table 50. The relevant information about overdose is presented in the current product label.

7.1.17 Postmarketing Experience

The Division of Drug Risk Evaluation, HFD-430, submitted a consult reviewing the Adverse Event Reporting System (AERS) database for all serious and non-serious pediatric adverse events reported between 12/31/98 and 08/10/06 for celecoxib. The search retrieved 88 cases, of which 31 spontaneous postmarketing reports were included in the case series. The age of patients ranged from 4 years of age to 17 years of age with the mean of 14 years. Of the 30 cases reporting gender, there were 18 females and 12 males. Celecoxib was most commonly used for pain, JRA, and tendonitis. Most of the adverse events were mentioned in only one report, except for rash (4), chest pain (3), hematochezia (2), and headache (2), all of which are labeled events.

7.2 Adequacy of Patient Exposure and Safety Assessments

The celecoxib development program included a total of 242 JRA patients with pauciarticular, polyarticular and systemic type JRA (without any active systemic features) in the single Phase 3 pivotal Study 195. Within Study 195, there were 77 patients exposed to low-dose celecoxib, 82 patients exposed to high-dose celecoxib and 83 patients exposed to naproxen, the active comparator, 15 mg/kg/day. There were two different celecoxib investigational suspensions developed for Study 195, a 50 mg/5 mL suspension for administering low-dose celecoxib (6 mg/kg/day) and a 100 mg/5 mL suspension for administering high-dose celecoxib (12 mg/kg/day).

Analysis by treatment group demonstrated that the JRA patients were reasonably balanced for demographic data and type JRA course. Race was incomplete in some of the CRFs and this reviewer concludes that not responding to this question may have been a parental preference. We do not have information as to why this question was unanswered. There is no discernable reason that this specific information is incomplete on the CRFs.

Caucasians were the predominant race enrolled in Study 195. There are more females than males enrolled in Study 195. This gender imbalance is a reflection of the higher incidence of pauciarticular JRA (5:1 ratio, female to male) and of polyarticular JRA (3:1 ratio, female to male) in females than in males.

Adverse events were representative of the labeled safety profile of non-selective NSAIDS and of COX-2 selective inhibitors in the majority of all adverse events reported in Study 195. See Section 7.1 Methods and Findings, Safety for explanation of the exposure and safety assessments. See Section 1.3.2 Efficacy and Section 1.3.4 Dosing Regimen and Administration for comments about the adequacy of patient exposure in relation to specific weight categories.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Section 7.1 Methods and Findings, Safety.

7.2.1.1 Study type and design/patient enumeration

See Section 6.1.4 Efficacy Findings, and Table 3 in the same section of this review.

7.2.1.2 Demographics

See Section 6.1.4, Efficacy Findings.

7.2.1.3 Extent of exposure (dose/duration)

See Section 7.1 Methods and Findings, and Tables 45 and 46.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were 3 clinical PK studies and 1 population PK study, which included an adult RA cohort of Study 195. There are no other studies submitted in this supplement.

7.2.2.2 Postmarketing experience

See Section 7.1.17 Postmarketing Experience of this review which cites a consult from the Division of Drug Risk Evaluation, HFD-430. There is no pediatric indication for celecoxib at this time. The Adverse Event Reporting System (AERS) database was searched for all serious and non-serious pediatric adverse events reported between 12/31/98 and 08/10/06 for celecoxib. The search retrieved 88 cases, of which, 31 spontaneous postmarketing reports were included in the cases series. The age of patients ranged from 4 to 17 years with the mean of 14 years of age.

7.2.2.3 Literature

The literature reviews are cited in the Sections in which the reference was noted.

7.2.3 Adequacy of Overall Clinical Experience

The celecoxib development program included a total of 242 JRA patients with pauciarticular, polyarticular and systemic JRA (without any active systemic features) in the single Phase 3 pivotal Study 195, a 12-week double-blind phase and a 12-week open-label extension phase. The data for study of the low-dose celecoxib is limited to 12 weeks. The data for high-dose celecoxib is limited to 24 weeks of study, including the 12-week phase open-label phase. In comparison to the two other non-selective NSAID/COX-2 selective inhibitors (VIOXX and MOBIC) approved by the Agency in the last two-and-a-half years, the data submitted in Study 195 is limited in overall clinical experience.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Celecoxib has been studied in juvenile animal models.

- **Gastrointestinal Effect:** In juvenile rats, treatment-related gastrointestinal toxicity (ulceration with peritonitis) was observed. It appears that juvenile rats are more sensitive to celecoxib-caused gastrointestinal toxicity than adult rats.
- **Skin Effect:** In juvenile dogs, treatment-related cutaneous/subcutaneous lesions (e.g., ulcerations) were observed. It appears that juvenile dogs are more sensitive to celecoxib treatment-induced dermal lesions.
- **Reproductive Tract Effect:** Possible treatment-related but not dose dependent gross lesions (unilateral or bilateral enlargement of testes and prominent tubules in the epididymal fat pad) and microscopic changes (minimal to slight unilateral or bilateral dilatation of seminiferous tubular dilatation and epididymal hypospermia) in all treated groups were reported. The significance of these reproductive findings is under review in the Agency. See the Pharmacology/Toxicology review by Gary Bond, PhD.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing in pediatric patients randomized to Study 195 was adequate except in the monitoring of blood pressure, systolic and diastolic. See Section 7.1.7 Laboratory Findings.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Safety monitoring of metabolic parameters was adequate in Study 195. See the Clinical Pharmacology review by Srikanth Nallani, PhD.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A large-scale (approximately 20,000 patients) medical outcome study (MOS) of the long-term cardiovascular and gastrointestinal safety is being conducted by Pfizer to assess the safety risks of long-term celecoxib therapy in adult patients with various conditions. See the MEMORANDUM, dated April 6, 2005, from John K. Jenkins, MD, through Steven Galson,

MD, M. P.H., to the NDA files 20-998, 21-156, 21-341 and 21-042, "Analysis and recommendations for Agency action regarding non-selective anti-inflammatory drugs and cardiovascular risk".

7.2.8 Assessment of Quality and Completeness of Data

The sponsor has adequately explained that a Pfizer monitor or appointed agent monitored the study through routine center visits to discuss the progress of the clinical trial and review the CRF data and original source documents with the study personnel for accuracy of data recording, study drug accountability, and correspondence. The investigator ensured that the trial participants were consented and made aware that personal information could be reviewed during the data verification process as part of monitoring/auditing processes by properly authorized agents of Pfizer or subject to inspection by regulatory authorities.

Informed Consent/Re-consent

The Division requested follow up information from the sponsor for the re-consent outcome for Study 195 which was prompted by the voluntary global market withdrawal of VIOXX (rofecoxib) due to the risk of serious adverse cardiovascular events. All study sites for Study 195 were informed of the requirement to re-consent all ongoing patients, as communicated by a "Dear Investigator" letter in December 2004.

Pfizer reported to the Division on October 6, 2006 that no adult patients and 74 juvenile patients were ongoing as of December 24, 2004. As explained by the sponsor, of the 74 juvenile patients, 72 were re-consented. Regarding the other 2 patients, 1 patient was re-consented verbally but continued on treatment beyond the IRB approval and the other juvenile patient was not re-consented.

7.2.9 Additional Submissions, Including Safety Update

THE 4-MONTH SAFETY UPDATE HAS BEEN RECEIVED AND WILL BE REVIEWED IN A SEPARATE DOCUMENT.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In Study 195, no deaths were reported. There were a total of 242 JRA patients randomized to 3 treatment groups, 77 patients in the low-dose celecoxib, 82 patients in the high-dose celecoxib and 83 patients in the naproxen, active comparator, group, respectively. Overall, the adverse event categories are representative of non-selective NSAID/COX-2 selective inhibitor safety profiles. Respiratory, thoracic and mediastinal disorders; eye disorders; and metabolic and nutrition disorders were the 3 body systems in which celecoxib, low-dose and high-dose, demonstrated more AEs than were reported in the naproxen group, across the total 24-week study.

In the respiratory, thoracic and mediastinal disorders body system, AEs were reported as cough, rhinorrhea, nasal congestion, wheezing, dyspnea exacerbated, epistaxis and snoring. There were 20 AEs in the low-dose celecoxib group, 32 AEs in the high-dose celecoxib group and 17 AEs in the naproxen group.

In the eye disorders system, AEs were reported as uveitis, blurred vision and conjunctivitis. There were 8 AEs in the low-dose celecoxib group, 5 AEs in the high-dose celecoxib group, and 4 AEs in the naproxen group.

In the metabolic and nutrition disorders body system, AEs were reported mild hyperuricemia, mild hypoglycemia and mild hyperglycemia. There were 3 AEs in the low-dose celecoxib group, 2 AEs in the high-dose celecoxib group and 1 AE in the naproxen treatment groups.

Overall, the total number of AEs reported across the 3 treatment groups was 804 events in the 24-week study. The most common AEs reported from the 3 treatment groups were: GI events (28%); infections and infestations (15%); nervous system (11%); and musculoskeletal, connective tissue and bone disorders (10%); respiratory, thoracic and mediastinal disorders (9%); general disorders and administration site conditions (8%); skin and subcutaneous tissue disorders (5%); investigations (3%); and eye disorders, injury and poisoning, blood and lymphatic system disorders, each as (2%).

Less commonly noted AEs and currently **unlabeled AEs** was one case of **disseminated intravascular coagulation (DIC) in systemic onset JRA**, and **prolonged activated partial thromboplastin time (APTT) documented** in 13, 12 and 4 patients treated with low-dose celecoxib, high-dose celecoxib and naproxen, respectively. T**witching** reported in one healthy adult who received celecoxib 200 mg as an oral suspension (20 mg/5 mL) and later received celecoxib 400 mg as an oral suspension (20 mg/5 mL) in Study 1162.

The most common laboratory adverse events were **elevated hepatic enzymes** without elevation of serum bilirubin in patients administered celecoxib. The highest elevation of liver enzymes was reported in a patient (high-dose celecoxib) who experienced acute CMV hepatitis and a severe flare of systemic JRA. She experienced marked elevation in liver enzyme and LDH values at Week 4 (ALT 545 U/L, AST 632 U/L, and LDH 657 U/L) resulting in hospitalization.
Within the vital signs, there was 1 patient in the naproxen treatment group reported to have an adverse event of hypertension. The protocol monitoring and threshold for measuring and reporting increases in systolic and/or diastolic blood pressure as an adverse event may have caused under reporting of blood pressure change in Study 195. The sponsor acknowledged that the monitoring of blood pressure effect in Study 195 was based on adult criteria and methodology. Hypertension is known to be commonly associated, in a dose-dependent manner, with the administration of non-selective NSAID/COX-2 selective inhibitor therapy in adult patients.

Patients with **systemic JRA** appear to be at **increased risk** for severe adverse events and SAEs in the setting of non-selective NSAIDS/COX-2 selective inhibitors. There were 22 patients (9%) in Study 195 with systemic onset JRA: 4 (5.2 %), 10 (12 %) and 8 (10 %) in the low-dose celecoxib, high-dose celecoxib and the naproxen groups. Overall, there were **5 patients (23%)**

with systemic onset JRA who experienced severe adverse events or SAEs, 1 of 4 (25%) in the low-dose celecoxib group, 2 of 10 (20%) in the high-dose celecoxib group, and 2 of 8 (25%) patients in the naproxen groups, respectively. The SAEs experienced by patients with systemic JRA demonstrated 1 of 4 (25%) in the low-dose celecoxib group (altered mental status, nausea, vomiting, elevated hepatic enzymes, abnormal coagulation laboratory tests, Cytomegalovirus (CMV) hepatitis), 2 of 10 (20%) in the high-dose celecoxib group (chest pain, myopericarditis, severe flare of JRA, abnormal coagulation laboratory tests; severe gastritis) and 2 of 8 (25%) in the naproxen treatment group (severe flare of JRA, abdominal pain, nausea, vomiting; hematuria and proteinuria). There appears to be a causal relationship between the study drug and abnormal coagulation laboratory tests. In the sub-group population of systemic onset JRA, elevation of PT, PTT, APTT could be the early stage of DIC. The occurrence of abnormal coagulation laboratory tests/DIC in patients with systemic onset JRA is documented in the pediatric literature (macrophage activation syndrome) and is a reported risk with administration of NSAIDs. **The current celecoxib label does not include the event of DIC or abnormal coagulation laboratory tests.**

Serious AEs occurred in a total of 9 patients across the 3 treatment groups. In the 12-week double-blind phase, there were a total of 5 patients with SAEs:

- **3** patients in the **low-dose celecoxib group** (SAEs reported as severe epigastric pain, acute viral illness requiring hospitalization and severe flare of JRA and acute CMV hepatitis) and
- **2** patients in the **high-dose celecoxib group** (SAEs reported as severe exacerbation of asthma on Day 1 of study drug, severe worsening of JRA).

In the 12-week open-label phase, there were 4 patients with SAEs:

- **1** patient in the **low-dose celecoxib group** switched to high-dose celecoxib (SAE reported as severe epigastric pain and vomiting post intentional overdose of erythromycin and celecoxib); and
- **3** patients in the **high-dose celecoxib group,** both study phases (SAE reported as nausea, vomiting, dehydration, fever, primary pulmonary tuberculosis; severe lymphadenopathy, pyrexia, sore throat requiring hospitalization; chest pain, inflammatory myopericarditis and severe flare of systemic JRA including positive DIC laboratory panel).

Severe adverse events prompting study withdrawal were:

- 1 patient with severe gastritis (**high-dose celecoxib group**),
- 1 patient with severe pruriginous allergic reaction (**low-dose celecoxib group**), and
- 1 patient with severe exacerbation of systemic JRA (**naproxen group**).

In the adult patients studied in the clinical PK or bioavailability study, the AE profile was consistent with the labeled adult safety profile with the exception of one unlabeled AE, **twitching** which was reported in 1 adult participant who received celecoxib suspension, **200 mg/day** and later received **400 mg/day.**

Of the total 242 JRA patients randomized in Study 195, 58 patients were administered low-dose celecoxib and 30 patients were administered high-dose celecoxib in total daily dosages as proposed in the JRA celecoxib label, 100 mg/day (weight 10 to 25 kg: 50 mg BID) or 200

mg/day (weight > 25 kg: 100 mg BID). **The balance of the patients in the celecoxib treatment groups received total daily dosages ≥ 200 mg/day which is higher than the adult RA labeled dose (starting dose as ~ 3.3 mg/kg/day to a maximum dose of 5.7 mg/kg/day)**. The following are examples of a celecoxib total daily dose using the proposed pediatric dose scheme:

- JRA patient who is 10 kg would receive celecoxib 10 mg/kg/day.
- JRA patient who is 13 kg would receive celecoxib 8 mg/kg/day;
- JRA patient who is 26 kg would receive celecoxib 7.6 mg/kg/day;
- JRA patient who is 37 kg would receive celecoxib 5.4 mg/kg/day.

Each of these examples raises concern that a pediatric patient would be exposed to higher celecoxib doses than are needed to achieve efficacy and, therefore, would be at greater risk for adverse events. **Body weight, rather than age, is the single most important predictive covariant for the apparent oral clearance of a drug and is important in pediatric dosing, particularly, when studying pediatric patients with a chronic disease such as JRA.** In pediatric chronic disease, patients are not infrequently smaller in weight and in height than their age-matched peers.

Children who receive higher doses of a non-selective NSAIDs/COX-2 selective inhibitors trend with a higher incidence of adverse events. There were **60 (23%), 85 (37%) and 66 (21%) AEs** reported in **patients less than 7 years of age** in the **low-dose celecoxib, high-dose celecoxib and naproxen groups**, respectively. **There are concerns that the proposed celecoxib pediatric dose scheme places undue safety risks for adverse events in this pediatric target population less than 7 years of age.** In adult studies with celecoxib, the adverse events and, specifically, the cardiovascular adverse events, specifically, thromboembolic, were more frequently seen with CELEBREX 200 mg BID (~5.7 mg/kg/day) dose than with the CELEBREX 100 mg BID dose (~3.3 mg/kg/day).

This reviewer stratified the 58 patients (treated with ≤ 200 mg/day), by body weight categories designated by the sponsor, and reports that there was an insufficient number of patients exposed to celecoxib suspension to adequately assess *efficacy and safety* at the proposed doses for JRA patients ≥ 10 kg to ≤ 12 kg and > 50 kg, and an insufficient number of patients to adequately assess *safety* in JRA patients with body weight ≥ 12 kg. Efficacy was demonstrated by sub-group analysis for patients who received the proposed celecoxib doses (100 mg or 200 mg/day).
The celecoxib study-doses in Study 195 were higher than the approved celecoxib starting doses for adult RA patients. There are concerns with the proposed dose scheme for celecoxib that the smallest weight patients would receive the highest celecoxib dose and, therefore, be at greater risk for more adverse events. See Tables 33 and 34.

Though the limited safety profile of AEs in Study 195 is consistent with non-selective NSAIDs/COX-2 selective inhibitors, **the exposure data for JRA patients at the proposed dosages (50 mg BID [100 mg/day] and 100 mg BID [200 mg/day])** are **insufficient to reach a robust conclusion about the safety in this target pediatric population for longer-term use of either celecoxib dose. The low-dose celecoxib was only studied for 12-weeks.**

Within the last three years, the Agency has approved one non-selective NSAID/COX-2 selective inhibitor, VIOXX (rofecoxib), based upon a total of 64 weeks of safety data and one semi-selective NSAID/COX-2 selective inhibitor, MOBIC (meloxicam), based upon a total of one 24-week study and two 52-week studies. The duration of Study 195 was 24-weeks (12-week double-blind with an optional 12-week open-label extension) which is less safety data than reported in previous pediatric non-selective NSAID/COX-2 selective inhibitor supplements. In the setting of increased safety information about the longer-term safety risks of non-selective NSAID/COX-2 selective inhibitor therapy, gastrointestinal and cardiovascular risk as the most prominent, Study 195 does not offer robust data to achieve a favorable decision to administer celecoxib to JRA patients.

There is demonstrated efficacy at the studied celecoxib doses of 100 mg to 600 mg/day and demonstrated **efficacy,** by non pre-specified **sub-group analysis**, at the lower proposed celecoxib doses of **100 mg to 200 mg/day**, by the JRA DOI 30 responder rate. During the Arthritis Advisory Committee, the **sponsor** presented **sub-group efficacy analyses** which demonstrated **efficacy** by the JRA DOI 30 in patients treated with **100 mg to 300 mg/day.**

The proposed JRA celecoxib dose scheme translates into doses, calculated as mg/kg/day, which are higher than the starting dose of ~ 3 mg/kg/day for adult RA (100 mg BID). **Actual celecoxib doses that are 25-30% above or below an intended prescribed celecoxib dose for pediatric patients create a safety risk. Based on the safety profile of celecoxib in this limited study, doses that may not be accurate, according to patient weight, may have clinically meaningful implications for safety.**

Clinical studies in adults with various conditions presented in the current **CELEBREX label report increased overall adverse events and, particularly, increased serious cardiovascular events, with increasing celecoxib doses.** Therefore, this reviewer concludes that though celecoxib has demonstrated efficacy at the proposed doses (100 mg or 200 mg/day) and demonstrated efficacy at the higher studied doses (> 200 mg to ≤ 600 mg/day), the amount of safety data is insufficient, as explained above, and the proposed dose scheme places children and adolescents with JRA at increased risk for adverse events.

The sponsor claims that an oral suspension was not feasible to produce in commercial quantities. The issue of a good faith effort on the part of the sponsor remains under review by CMC for a final decision. It is recommended that the sponsor consider additional Phase 3 study of celecoxib in JRA patients for at least 52 weeks duration and consider the development of a lower strength formulation (e.g., a 25 mg capsule sprinkle) which would improve the accuracy of pediatric dosing.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was one Phase 3 pivotal Study 195. Therefore, there was no Integrated Safety Summary in Supplement 021. Adult RA safety data from the PK studies was reviewed and summarized in this review.

7.4.1.1 Pooled data vs. individual study data

The database included all randomized patients in one trial, Study 195. Safety also included the adult RA patients who participated in the population PK study and the healthy adult participants who were randomized in the clinical PK studies. Sub-analyses, within the JRA patient population from Study 195, were performed to assess specific questions about the 1) efficacy with and without the concomitant administration of methotrexate, 2) efficacy as measured by the JRA DOI 30, in a small subset of patients [stratified by weight categories as defined by the sponsor] treated with the proposed celecoxib doses as in the proposed label were performed by this reviewer. These sub-analyses from small pooled data was completed recognizing that the pre-specified protocol was not designed to test a hypothesis about sub-analyses or exploratory analyses beyond the protocol.

7.4.1.2 Combining data

See Section 6.1 Efficacy, sub-analyses of pooled efficacy data in JRA patients treated with celecoxib < 200 mg/day [celecoxib dosage as proposed by the sponsor].

7.4.2 Explorations for Predictive Factors

There were no pre-specified additional explorations for predictive factors. This response applies to Section 7.4.2.1 through Section 7.4.2.5.

7.4.2.1 Explorations for dose dependency for adverse findings

See comment above.

7.4.2.2 Explorations for time dependency for adverse findings

See comment above.

7.4.2.3 Explorations for drug-demographic interactions

See comment above.

7.4.2.4 Explorations for drug-disease interactions

See comment above.

7.4.2.5 Explorations for drug-drug interactions

See comment above.

7.4.3 Causality Determination

The conclusions about causality are discussed in Section 7.1. Safety Findings

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor proposes to administer celecoxib (capsules) to JRA patients based on their body weight: 50 mg BID (100 mg/day) for patients with body weight ≥ 10 kg to ≤25 kg; and 100 mg BID (200 mg/day) for patients with body weight > 25 kg. The dosage and administration as proposed by the sponsor does not include consideration of dose escalation from the lowest recommended dose to the maximum dosage as proposed. As concluded in this review, the patient exposure data is insufficient to assess safety in specific weight groups and insufficient to adequately assess long-term safety of non-selective NSAIDs/COX-2 selective inhibitors in patients with JRA. **The studied celecoxib dose scheme includes doses 2 to 4 times the adult approved doses for RA.** See the Summary for Efficacy and the Summary for Safety of Study 195. See the Clinical Pharmacology review by Atul Bahattaram, PhD and Srikanth Nallani, PhD.

8.2 Drug-Drug Interactions

Drug-drug interactions in JRA patients should include analysis of concomitant medications that are commonly used in this target population such as non-selective NSAIDs, DMARDs, Biologic Response Modifiers (BRMs) and immunosuppressant therapy. The eligibility criteria in Study 195 included the appropriate NSAID, DMARDs, BRMs and immunosuppressant medications. This reviewer completed sub-analyses, to the extent possible as the pre-specified protocol did not include these type sub-analyses, to assess if there were any differences in outcome. See Section 6.1 Efficacy Findings. Also see the Clinical Pharmacology reviews by Srikanth Nallani, PhD. and Atul Bhattaram, PhD.

8.3 Special Populations

Adult special populations were studied and reported in the original NDA 20-998 submission for CELEBREX (celecoxib). The current product label includes special population information for geriatric age persons, individuals of different race, individuals with hepatic insufficiency, and individuals with renal insufficiency. Celecoxib is not approved for use in pediatric patients. The

prescribing of non-selective NSAID/ COX-2 selective inhibitors in pediatric patients should be managed cautiously in these patients who may also be receiving concomitant non-selective NSAIDs, DMARDs, BRM and or an immunosuppressant agent. Smaller weight pediatric patients must be prescribed non-selective NSAID/COX-2-selective inhibitors with caution, particularly with consideration for those patients with renal impairment, hepatic insufficiency and potential allergic skin or hypersensitivity reactions, or asthma.

8.4 Pediatrics

NDA 20-998, Supplement 021 Study 195 represents the third application with a non-selective NSAID/COX-2 selective inhibitor proposed for the treatment of the signs and symptoms of JRA received by the Agency in the last 3 years. Recruitment of JRA patients is challenging, particularly in the younger age group and is becoming increasing more difficult as more clinical trials in JRA are being conducted.

Study 195 included 10% of the total randomized patients as systemic course JRA (without any active systemic features). Patients in the systemic JRA group experienced intravascular coagulopathy /DIC events across the 3 treatment groups in Study 195. In Study 195, there were **5 patients (23%) with systemic onset JRA who experienced SAEs**, 1 of 4 (25%), 2 of 10 (20%), and 2 of 8 (25%) patients, in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups, respectively. DIC is an unlabeled event in the current celecoxib label.

In the Division of Drug Risk Evaluation, HFD-430, through a Consult to the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), one of the notable unlabeled adverse events included the report was of a 17-year-old female who experienced increased abdominal pain, mildly increased liver enzymes and persistent urinary tract infection which led to hospitalization. She received levofloxacin 500 mg QD and celecoxib 200 mg QD. She experienced DIC and multi-organ failure. The events were possibly causally related to levofloxacin and celecoxib co-administration. See Section 1.3.1 Brief Overview of the Clinical Program.

8.5 Advisory Committee Meeting

An Arthritis Advisory Committee meeting was held on November 29, 2006 to discuss the risks and benefits of the safety of non-selective NSAIDs/COX-2 selective inhibitors in adult patients with various conditions and in pediatric patients with JRA, in view of the reported severe adverse cardiovascular risk of long-term therapy with this class of drugs. Severe adverse cardiovascular events have been reported from 18-month study of non-selective NSAID/COX-2 selective inhibitors. The overall conclusions from the AAC meeting were the following:

- Efficacy is demonstrated at the studied doses and appears to be demonstrated at the lower proposed doses;
- Safety has not been demonstrated in the limited safety data base of 24-weeks. The vote was 8 to 7 with one abstention that the current data do not demonstrate that celecoxib is safe in JRA. The AAC remains unclear if celecoxib is safe to administer longer-term in children with JRA.

- The proposed dose scheme recommends the highest dose to the smallest weight patients. The Committee expressed concern about the safety risks of the proposed dose scheme, in general, and, particularly, for the smaller weight patients. The Committee was favorable toward the dosing frequency of twice-a-day. The Committee inquired if a 25 mg formulation was considered for more accurate dosing in pediatric patients and inquired about the absence of a proposed suspension formulation for the proposed pediatric indication though a suspension formulation was investigated.
- The pediatric rheumatology community recommended increasing the choices of approved drugs for the indication of JRA.
- The AAC would like to see Celebrex approved (vote of 15 in favor and 1-opposed), recognizing that the safety is inadequate as studied, and strongly clarified this cautionary recommendation for approval with the request that a robust monitoring process, albeit a registry, for celecoxib safety and outcomes, in general, be established if the Agency approves the supplement. The stakeholders, for developing the content and process of such proposed monitoring, varied among the FDA, the National Institutes of Health, the Centers for Disease Control, industry and professional subspecialty organizations composed of pediatric rheumatologists.
- The AAC questioned if an approval could be limited to an indication of 24-weeks due to the limited safety information. The AAC questioned how such an approval could affect the wider use of celecoxib in children and adolescents with other conditions such as orthopedic diagnoses and pain conditions.

8.6 Literature Review

The literature reviews are cited in the Sections in which the reference is noted.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan does not apply to this supplement at this time.

8.8 Other Relevant Materials

Within the last three years, the Agency has approved one non-selective NSAID/COX-2 selective inhibitor, VIOXX (rofecoxib), approved August 2004, in JRA patients for the treatment of the signs and symptoms of pauciarticular and polyarticular JRA in patients≥ 2 years to ≤ 17 years of age, and one semi-selective NSAID/COX-2 selective inhibitor, MOBIC (meloxicam), approved August 2005, for the treatment of the signs and symptoms of JRA in patients aged 2 through 17 years, when added to standard background therapy. The **meloxicam JRA patient data** included **two studies, one 24-week study and one 52-week study** as well as **an open-label study, 52 week study**. The **rofecoxib JRA patient data** included **two studies, one 12-week study and one 9-month extension study, for a total of 52 weeks.**

Both the rofecoxib and meloxicam pediatric development program study designs in JRA included two common features: 1) the JRA DOI 30 (ACR PED 30) was used as the primary endpoint for efficacy in both studies, and 2) naproxen was the active comparator in both studies.

The rofecoxib study used the non-inferiority study design with a pre-specified margin of ≥ 0.50 (95% CI). The Division, specified in the pediatric WR, that a lower limit margin of the point estimate≥ 0.50 (95% CI) was too low to support a finding of efficacy based on non-inferiority trail design. The rofecoxib review was conducted using a lower limit margin of ≥ 0.75. Only the high-dose of rofecoxib achieved non-inferiority to naproxen. VIOXX (rofecoxib), oral suspension and tablets, was approved at the higher of the two study doses, 0.6 mg/kg/day to a maximum dose of 25 mg, once per day. MOBIC (meloxicam), oral suspension and tablets, was approved as 0.125 mg/kg/day and 0.250 mg/kg/day. In the meloxicam study (107.235) sample size was sufficient to ensure a one-sided alpha 0.05 non-inferiority for a difference of 0.20 in proportion responding with a power of 80%.

VIOXX (rofecoxib) was voluntarily withdrawn from the global market by Merck on September 30, 2004 following the observation of an increased risk of serious adverse CV events compared to placebo in a 18-month long-term controlled clinical trial. Subsequent to that action, reports of additional data from controlled clinical trials became available for other non-selective NSAIDs/COX-2 selective inhibitors that also demonstrated an increased risk of serious adverse CV events compared to placebo. These new data prompted the Agency to conduct a comprehensive review of the available data and to present the issue for review to a joint meeting of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees held February 2005.

On April 6, 2005, the Agency concluded that the 3 approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with increased risk of serious adverse cardiovascular (CV) events compared to placebo.

The 3 approved COX-2 selective drugs reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs. Only rofecoxib has been shown to reduce the risk of serous GI bleeding compared to a non-selective NSAID (naproxen) following chronic use. The overall benefit of COX-2 selective drugs in reducing the risk of serious GI bleeding remains uncertain, as does the comparative effect of COX-2 selective NSAIDs and other strategies for reducing the risk of GI bleeding following chronic NSAID use (e.g., concomitant use of a non-selective NSAID and a proton pump inhibitor).

Valdecoxib is associated with an increased rate of serious and potentially, life-threatening skin reactions, (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme), compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of nay demonstrated advantage over other NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing. At the recommendation of the Agency, Pfizer formally withdrew BEXTRA (valdecoxib) from the U.S. market as of April 2005.
The professional labeling for all prescription NSAIDs were revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning includes the well described NSAID class risk of serious, and often life-threatening G bleeding, which was previously contained in a bold warning.

The data from controlled clinical trial comparison of COX_2 selective and non-selective NSAIDs do not clearly demonstrate an increased relative risk for the COX-2 selective drugs, despite the substantial size of these studies. Despite the limitations of the available data, overall, there is evidence, principally, from a small number of placebo-controlled trials, that the approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, valdecoxib) are associated with an increased risk of serious adverse CV events (e.g., myocardial infarction, stroke, death).

Recommendations from the Agency included patient labeling for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, inclusion of a Medication Guide for the approved product remaining on the market; NSAIDs as a class, include a Boxed Warning and contraindications section in the product label explaining the potential CV risks of events; CELEBREX (NDA 20-998/NDA 21-156 (celecoxib capsules) label include a boxed warning and other labeling changes; and that the Center for Drug Evaluation and Research (CDER) request a written commitment form the sponsor to conduct an additional long-term study (or studies) to address the safety of celecoxib compared to naproxen and other appropriate active controls (e.g., other non-selective NSAIDs, appropriate non-NSAID active comparators).

The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events had been demonstrated for celecoxib.

Note: Information in this section, other than the comments about the rofecoxib and meloxicam pediatric development programs, is extracted from a MEMORANDUM, April 6, 2005 from John K. Jenkins, MD, Director of the Office of New Drugs (OND) and Paul J. Seligman, MD, PhD, Director, Office of Pharmacoepidemiology and Statistical Science (OaPaSS) through Steven Galson, MD, PhD, Acting Director, Center for Drug Evaluation and Research, to the NDA files 20-998, 21-156, 21-341 and 21-042. The MEMORANDUM subject is the Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk.

9 OVERALL ASSESSMENT

9.1 Conclusions

The high-dose celecoxib oral suspension, 6 mg/kg/day (3 mg/kg BID) and the low-dose celecoxib oral suspension, 12 mg/kg/day (6 mg/kg BID) achieved non-inferiority to naproxen oral suspension, 15 mg/kg/day (7.5 mg/kg BID) as 125 mg/5 mL for the treatment of the signs and symptoms of JRA in patients ≥ 2 years of age and ≤ 17 years by demonstrating efficacy at the lower point estimate -.25 margin for non-inferiority. Two different strengths of oral investigational suspension celecoxib, 50 mg/5 mL and 100 mg/5 mL, to study low-dose and high-dose celecoxib, respectively, were developed by the sponsor for Study 195.

Within the non-inferiority study design of Study 195 (12-week randomized, double-blind, multicenter, active-controlled, parallel-group and an optional 12-week open-label extension with

high-dose celecoxib oral suspension: 24-weeks total), the primary endpoint for evaluating efficacy was the proportion of patients meeting the Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30% (JRA DOI 30). The proportion of patients meeting the JRA DOI 30 criterion over the 12-week phase was 69%, 80% and 67% in the low-dose celecoxib, high-dose celecoxib and naproxen treatment groups. This medical reviewer has over 15 years clinical practice experience with naproxen oral suspension and has observed this formulation of naproxen to demonstrate consistent clinical improvement in all course-types of JRA. Therefore, the non-inferiority margin, as defined in the protocol, appears acceptable based on these personal years of pediatric rheumatology clinical experience with naproxen in the target population.

Pfizer proposes celecoxib dosage (50 mg capsule) and administration based on body weight of JRA patients: 50 mg BID (100 mg/day) for patients ≥ 10 kg to ≤ 25 kg and 100 mg BID (200 mg/day) for patients > 25 kg. The exposure data submitted in Study 195 is insufficient to 1) adequately assess *efficacy and safety* of celecoxib suspension in the proposed dosages for JRA patients with body weight 10 kg to 12 kg, and > 50 kg and 2) insufficient to adequately assess *safety* at the proposed doses in JRA patients with body weight ≥ 10 kg to ≤ 50 kg. The study of high-dose celecoxib, 12 mg/kg/day, a dosage not proposed for administration to JRA patients, was studied for 12-weeks in the double-blind phase and for an additional 12-weeks in an open-label extension phase. The study of low-dose celecoxib was limited to 12-weeks duration in the double-blind phase.

As noted in the Guideline, ICH E1: The Extent of Population Exposure to Assess Clinical Safety, there is general agreement for the following: "…100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. …Data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. Though the limited safety profile in Study 195 is consistent with non-selective NSAIDs/COX-2 selective inhibitors, **the exposure data for JRA patients at the proposed dosages (50 mg BID [100 mg/day] and 100 mg BID [200 mg/day])** are **insufficient to reach a robust conclusion about the safety in this target pediatric population for longer-term use of either celecoxib dose, low-dose or high-dose.**

This reviewer concludes that there is adequate evidence of efficacy, based on the overall data analysis of all treated patients and based on the sub-group analysis of JRA patients treated at the proposed dosages. The proposed celecoxib dose scheme, in mg/kg/day, for JRA patients includes daily doses higher than the starting dose and the maximum approved dose for adults with RA. There is concern that the proposed dose scheme places children and adolescents with JRA at increased risk for adverse vents when efficacy is demonstrated at lower doses which appear to be safer in this limited safety data base.

The Agency has concluded that "despite the limitations of the available adult data, overall, there is evidence, principally, from a small number of placebo-controlled trials, that the approved non-selective NSAIDs/COX-2 selective inhibitors (i.e., celecoxib, rofecoxib, valdecoxib) are associated with an increased risk of serious adverse cardiovascular events (e.g., myocardial infarction, stroke, death)". These specific adult serious adverse cardiovascular events refer to

thromboembolic events as myocardial infarction and cerebrovascular accidents which are rare in children beyond the clinical setting of hypercoagulable or hyperlipidoses conditions.

In view of the shorter duration of Study 195 (12-weeks with the low-dose celecoxib and high-dose celecoxib and additional 12-weeks with an open-label study of high-dose celecoxib) compared to more than 52 weeks safety data and more than 2 years safety data, respectively, from two other non-selective NSAID/COX-2 selective inhibitor supplements in JRA patients approved by the Agency in the last two-and-a-half years, and the limited safety data in the proposed celecoxib dosage range, the safety data submitted precludes reaching an adequate safety assessment in this target population of pediatric patients with JRA.

In consideration and support of the need for expanded approved drugs for the indication of the relief of the signs and symptoms of JRA, recommendations to Pfizer are cited in Section 9.5 Comments to Applicant of this review.

9.2 Recommendation on Regulatory Action

The recommended regulatory action is approvable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

As there is not a pediatric indication at this time, there is no risk management activity for this subpopulation.

9.3.2 Required Phase 4 Commitments

There are no Phase 4 commitments at this time.

9.3.3 Other Phase 4 Requests

There are no Phase 4 requests at this time.

9.4 Labeling Review

TO BE SUBMITTED AS A SEPARATE DOCUMENT.

9.5 Comments to Applicant

Additional Phase 3 study with celecoxib in JRA patients is recommended.

- The study design treatment conduct section of a Phase 3 protocol should include the study of the proposed doses, across the intended patient weight groups which would be recommended in the label for clinical prescribing in JRA patients.
- The formulation of a lower dose unit should be considered for the following rationale:
  1. To support more accurate dosing of these pediatric patients and,
  2. In consideration of the trend of increased adverse events with high-dose compared to low-dose celecoxib as demonstrated in Study 195.
- Longer-term safety study and longer-term monitoring should be included in the final study design to extend to at least one-year or longer, based on the reports of the increased serious adverse cardiovascular safety events, specifically thromboembolic events as myocardial infarction and cerebrovascular stroke reported from 18-month study of drugs in this pharmacologic class, non-selective NSAID/COX-2 selective inhibitor drugs.
- The consideration of a process to successfully establish a monitoring process, albeit a registry, to follow pediatric patients, not only patients with JRA but in pediatric patients with other diagnoses who may be treated with celecoxib, to better understand the long-term safety.

10 APPENDICES

10.1 Review of Individual Study Reports

Protocol for Study 195

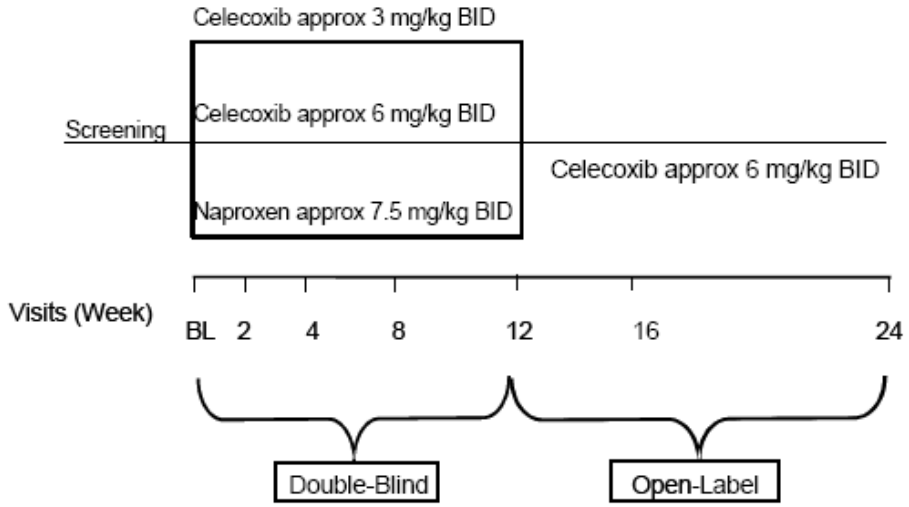
Study Title
"A Randomized, double-blind, Multicenter, Active-controlled Parallel-Group Study to Evaluate the Efficacy and Safety of Celecoxib Suspension Compared to Naproxen Suspension in Patients with JRA"

Primary Objective
1. To evaluate the efficacy and safety of celecoxib suspension for the treatment of the signs and symptoms of JRA as compared to naproxen suspension (a standard comparator).

Secondary Objectives
1. To compare the PK profile of celecoxib suspension in children with JRA to an adult cohort with rheumatoid arthritis;
2. To obtain pharmacokinetic information to guide the dosing of celecoxib in the pediatric population; and
3. To evaluate various Definitions of Improvement (DOI) for use in the JRA population (JRA DOI-30, JRA DOI 50 and JRA DOI 70 in pauciarticular course JRA and polyarticular course JRA, separately).

Study Design
This study was designed as a 12-week, randomized, double-blind, active-controlled, parallel-group, multicenter, non-inferiority study comparing the efficacy and safety of celecoxib suspension to naproxen suspension in patients with JRA, with an optional 12-week open-label treatment phase. See Figure 1.

Figure 1. Study Design for Protocol N49-01-02-195, Study 195: Double-Blind Phase and Open-Label Phase. (Sponsor's Figure 1, page 30 of 4701)



The patients who met the eligibility criteria for Study 195 were randomly assigned to one of three treatment groups: Celecoxib 50 mg/5mL oral suspension (target dose: 3 mg/kg BID), celecoxib 100 mg/5mL oral suspension (target dose: 6 mg/kg BID), or naproxen oral suspension 125mg/5 mL (target dose 7.5 mg/kg BID) in a 1:1:1 ration. Patients who completed the 12-week double-blind treatment period were eligible to participate in the open-label treatment phase.

Patients who elected to enter the open-label phase received celecoxib 100 mg/5 mL oral suspension (approximately 6 mg/kg BID) for 12 weeks. The volume of study medication administered was determined by the patient's weight at the Week 12 visit. Study medication was taken BID, before breakfast and before bedtime in both phases of Study 195.

The purpose of this study was to obtain safety and efficacy experience with celecoxib in patients with polyarticular and pauciarticular JRA. For ethical reasons, this study was not to include a placebo arm or a flare design. Due to the pediatric population, it was not to be recommended to require worsening of a patient's signs and symptoms prior to allocation to a treatment group. The active comparator, naproxen, is approved for and commonly prescribed in pediatric patients with JRA. The selection of naproxen, a nonselective NSAID (COX-1/COX-inhibitor), as an active comparator permitted the safety and efficacy results of celecoxib to be analyzed in the context of a currently approved therapy with a pediatric indication for the relief of signs and symptoms of JRA. Tolerability and durability of celecoxib in the longer-term treatment was assessed in an open-label extension 12-week study.

Study Treatment - Double-Blind Phase
As explained by the sponsor, patients with JRA were to be randomized to 1 of 3 treatments: Celecoxib 50 mg/5 mL oral suspension (delivering a target dose of 3 mg/kg BID), celecoxib 100 mg/5 mL oral suspension (delivering a target dose of 6 mg/kg BID), or naproxen 125 mg/5 mL oral suspension (delivering a target dose of 7.5 mg/kg BID). For ease of administration, patients were to be assigned to a fixed dose of suspension at Baseline (double-blind phase) and at Week

12 (open-label phase) dependent upon the patient's weight at those visits. The dose, to be assigned at the Baseline and Week 12 visits, was not to change during each phase of the study, even if the patient's weight subsequently changed. The sponsor administered the dosage based on the volume of the suspension. See Table 63 for the dosage for each treatment arm by the patient's weight.

Table 63. Dosage Based on Volume: Patients with JRA (Sponsor Table 5, page 43 of 4701)

Weight	Celecoxib Low-Dose Suspension (3 mg/kg BID)	Celecoxib High-Dose Suspension (6 mg/kg BID)	Naproxen Suspension (7.5 mg/kg BID)
9-12 kg	25 mg BID (50 mg TDD)	50 mg BID (100 mg TDD)	62.5 mg BID (125 mg TDD)
13-25 kg	50 mg BID (100 mg TDD)	100 mg BID (200 mg TDD)	125 mg BID (250 mg TDD)
26-37 kg	75 mg BID (150 mg TDD)	150 mg BID (300 mg TDD)	187.5 mg BID (375 mg TDD)
38-50 kg	100 mg BID (200 mg TDD)	200 mg BID (400 mg TDD)	250 mg BID (500 mg TDD)
>50 kg	150 mg BID (300 mg TDD)	300 mg BID (600 mg TDD)	500 mg BID (1000 mg TDD)

Note: Celecoxib Low-Dose Suspension = 50 mg/5 mL; Celecoxib High-Dose Suspension = 100 mg/5 mL; Naproxen Suspension = 125 mg/5 mL.
Abbreviations: BID = Twice Daily; TDD = Total Daily Dose; mg = Milligram; kg = Kilogram; mL = Milliliter.

Study Treatment - Open-Label Extension Phase
All patients who elected to continue in the open-label phase of the study will be started with open label celecoxib 6 mg/kg BID oral suspension on the day following the Week 12 visit. The patient's weight was to be recorded at the Week 12 visit and this weight was to be used to determine the appropriate dose for a patient in the open-label phase, according to the following algorithm:

- 9-12 kg = 2.5 mL celecoxib oral suspension (100 mg/5 mL) BID
- 13-25 kg = 5 mL celecoxib oral suspension (100 mg/5 mL) BID
- 26-37 kg = 7.5 mL celecoxib oral suspension (100 mg/5 mL) BID
- 38-50 kg = 10 mL celecoxib oral suspension (100 mg/5 mL) BID
- > 50 kg = 15 mL celecoxib oral suspension (100 mg/5 mL) BID

Study Treatment - Adult Patients with Rheumatoid Arthritis
All adult patients with RA were to receive 1 bottle containing sufficient celecoxib 100 mg/5 mL oral suspension to last at least 18 days. All adult patients RA subjects were to be instructed to take 200 mg (10 mL) of celecoxib suspension BID for 14 days.

Concomitant Medications
As described by the sponsor, the patients were to be instructed to avoid use of any medication other than the drugs provided for in Study 195.
1. NSAIDs were to be discontinued >5 half-lives, or a minimum of 48 hours, whichever was greater, prior to the Baseline visit. Patients were to have discontinued rofecoxib, oxaprozin, and/or piroxicam 4 days prior to the Baseline Visit. NSAIDs were to be prohibited during study participation.
2. Oral corticosteroids were to be prohibited unless the patient was receiving a dose of

≤0.2 mg/kg/day (or 10 mg/day of prednisone equivalent dose, whichever was less). A stable dose was to be required for >4 weeks duration prior to Screening. Dose adjustments were to be prohibited during study participation. Injectable corticosteroids or IA injection of hyaluronic acid were also to be prohibited, (patients could receive a single joint injection after they had completed the double-blind period, if necessary);
3. Analgesics and antipyretics (acetaminophen up to 50 mg/kg/day could be taken for reasons other than arthritis, only if absolutely necessary, and for no more than 3 consecutive days, and were to be avoided within 24 hours prior to arthritis assessments performed at any visit.) If the patient needed to use an analgesic or antipyretic, its use was to be record on the appropriate CRF. Patients were not to use an analgesic for relief of arthritis symptoms.
4. Methotrexate was to be prohibited in doses exceeding 1 mg/kg/day (or exceeding a maximum allowable weekly dose of 40 mg). Patients were to have received a stable dose for >8 weeks prior to Screening, and were not to have a dose adjustment during study participation.
5. Anti-ulcer drugs (eg, prostaglandins, mucous protectants, proton pump inhibitors, or H2 receptor antagonists) were to be prohibited. Occasional use of antacids, sucralfate and over the counter H2 receptor antagonists was to be permitted for relief of GI symptoms provided that use was to be captured on the appropriate CRF.
6. Sulfasalazine was to be allowable in doses up to 3 grams/day. Patients were to have received a stable dose for 12 weeks prior to the Screening visit.
7. Anticoagulants/anti-platelet agents could be used if, in the Investigator's opinion, the clinical benefits of study drug therapy would outweigh the risk of potential bleeding.
8. Lithium agents were to be prohibited.
Dietary recommendations were to be at the discretion of the Investigator. Whenever possible, the patient's usual and customary diet was to be continued.

Adult Patients with Rheumatoid Arthritis
The following drugs were to be specifically excluded for adult patients with RA:
1. NSAIDs were to be discontinued >5 half-lives, or a minimum of 48 hours, whichever was greater, prior to the Baseline visit. Patients were to have discontinued rofecoxib, oxaprozin, and/or piroxicam 4 days prior to the Baseline visit. NSAIDs were to be prohibited during study participation.
2. Methotrexate was to be prohibited in doses exceeding 25 mg/week. A stable dose was to be required >8 weeks prior to Screening.
3. Oral corticosteroids were to be prohibited unless the patient was receiving a dose of ≤ 10 mg/day of prednisone or equivalent. A stable dose was to be required for 12 weeks prior to Screening. Dose adjustments were to be prohibited during study participation. Injectable corticosteroids or IA injection of hyaluronic acid were not to be administered within 4 weeks prior to the Screening visit and were to be prohibited during study participation.

Study Schedule of Visits – Patients with Juvenile Rheumatoid Arthritis

Table 64 presents the schedule of observations and events for the double-blind and open label extension phase of Study 195. Follow-up clinical assessments were performed at Week 2, 4, 8, and 12 in the double-blind phase and at Weeks 12 and 24 in the open-label extension phase with limited assessment of specific protocol activities at Week 16. See Table 64.

Table 64. Study Schedule Visit Flow Chart for Patients with JRA (Study 195)
(Sponsor Table 1, page 32 of 4701)

Protocol Activities and Forms to be Completed	Pretreatment		Double-Blind			Open-Label		
	Screening (Day)	Baseline (Day)	Treatment (Week)			Week		
	-14 to -3	Day 1	2 (±2 Days)	4 (±2 Days)	8 (±3 Days)	12 (or Early Termination) (±3 Days)	16 (±3 Days)	24 (or Early Termination) (±3 Days)
Informed Consent[a]	X							
Randomization		X						
Medical History[b]	X	X						
Physical Examination[c]	X				X	X		X
Vital Signs	X	X	X	X	X	X	X	X
Height and Weight		X				X		X
Slit Lamp Exam[d]		X				X		X
Clinical Laboratory Tests[e]	X		X	X	X	X	X	X
C-Reactive Protein (CRP)	X		X	X	X	X		X
Blood Samples for Pharmacokinetic Analysis[f]			X	X	X	X		
Joint Assessments[g]	X	X	X	X	X	X		X
Physician's Global Assessment of Disease Activity[h]	X	X	X	X	X	X		X
Parent's Global Assessment of Overall Well-Being (CHAQ Subsection)[h]	X	X	X	X	X	X		X
Parent's Assessment of Physical Function (CHAQ Disability Index)[h]		X	X	X	X	X		X
Parent's Assessment of Child's Arthritis Pain (CHAQ Subsection)[h]		X	X	X	X	X		X
PedsQL™ Inventory		X				X		X
Adverse Event Review[i]			X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X
Dispense Study Medication		X		X	X	X[j]	X	
Drug Return			X	X	X	X	X	X

[a] Informed consent for JRA subjects was given by the subject's parent or legal guardian before any study-related procedures were performed. When appropriate, subjects were asked for their assent prior to participation. The Informed Consent Form (ICF) was not collected on the CRF.
[b] At each visit where a medical history or physical examination was performed, a developmental evaluation was performed. At the Baseline visit, the medical history was reviewed. Changes from the Screening visit were recorded on the "Study Specific Medical History and Physical Examination" form or the "Additional Medical History" form as appropriate.
[c] Physical exam including dermatologic and developmental evaluations. Physical examination findings at Weeks 8, 12, and 24 were captured only in the source documentation. Clinically significant changes from Screening were captured as adverse events, if deemed appropriate by the Investigator.
[d] The Baseline slit lamp exam was performed at any time within the Screening window provided the results were available to the Investigator prior to randomization of the subject at the Baseline visit. The slit lamp exam required at Weeks 12 and 24 were performed within the designated visit window.
[e] Clinical laboratory tests included hematology, biochemistry, and urinalysis as defined in the protocol. JRA female subjects of childbearing potential had a urine pregnancy test at every visit. Childbearing-potential was defined as menarche or ≥10 years of age, whichever occurred sooner. Urine pregnancy test results were not collected on the CRF. A DIC panel was collected at any time a JRA subject experienced a systemic flare.
[f] A single PK sample was drawn at Weeks 2, 4, 8, and 12/Early Termination, concurrent with blood sampling for other labs. The last digit of the subject's randomization number determined the PK sampling time. Subjects with randomization numbers ending in an even digit had the visit/sample time sequence of predose (trough) and 0.5, 3, and 6 hours postdose, while subjects with randomization numbers ending in odd digits had the visit/sample time sequence 6, 3, and 0.5 hours postdose and predose (trough) at Weeks 2, 4, 8, and 12, respectively.
[g] Joint Assessments included swollen joint counts, number of tender/painful joints, and number of joints with limited motion.
[h] The rater was to be consistent throughout the trial.
[i] At the Baseline Visit, the diary card was dispensed to the subject/parent.
[j] Medication for the open-label phase was dispensed at this visit if the subject/parent elected to continue study participation. The site contacted IVRS to continue the subject in the open-label phase of the study.

Adult Patients with Rheumatoid Arthritis

In Study 195, there was an adult cohort with RA who participated in a 2-week, assigned, open-label study. As explained by the sponsor, the PK profile of celecoxib suspension was compared in children with JRA (from the pediatric cohort described herein) versus the PK profile in the adult cohort who took celecoxib 200 mg BID as 100 mg/5 mL suspension. The study schedule visits for the adult study are presented in Table 65.

Table 65. Adult RA Study Schedule of Visits (Sponsor Table 2, page 34 of 4701)

Protocol Activities and Forms to be Completed	Screening Day -14 to -3	Baseline Day 1	Week 2 (or Early Termination) (±2 Days)
Informed Consent[a]	X		
History and Physical Examination[b]	X		X
Clinical Laboratory Tests[c]	X		
Urine Drug Screen Test (including ethanol [EtOH])	X		
12-Lead Electrocardiogram (ECG)	X		
Discontinue NSAIDs/Salicylates	X		
Blood Samples for Pharmacokinetic Analysis[d]		X	X
Adverse Event Review			X
Concomitant Medication Review	X	X	X
Dispense Study Medication		X	
Return and Drug Accountability			X

[a] Informed consent form (ICF) was signed by the subject before any study related procedures were performed. ICF was not collected on the CRF.

[b] Physical examination without history at Week 2. The Week 2 physical examination was captured in source documentation only. Clinically significant changes from Screening were captured as adverse events, if deemed appropriate by the Investigator.

[c] All female subjects of childbearing potential (and up to 2 years post-menopausal) had a serum pregnancy test to ensure a negative test result. A blood sample for Hepatitis B surface antigen was collected from all subjects. Clinical laboratory results were not collected on the CRF.

[d] PK samples were taken at 0 hours predose at Baseline, and steady state PK samples were drawn at 0 hours predose (trough), 0.25, 0.5, 1, 2, 4, and 6 hours postdose at the Week 2 visit.

Eligibility Criterion

JRA Inclusion Criteria

1. Patients were to have a diagnosis of polyarticular or pauciarticular course of JRA as determined by the American College of Rheumatology (ACR) criteria. Patients with systemic onset JRA who had polyarticular or pauciarticular course were to also be eligible. Subjects with active systemic features were not to be entered.
2. Patient was to be at least 2 years of age and had not yet reached his/her 17th birthday prior to the Baseline visit. Onset of JRA must have occurred prior to the subject's 16th birthday.
3. Patients were to weighed at least 9 kg.
4. Patients were to have had ≥ 1 swollen joint and ≥ 1 joint with limitation of motion. Joints with limited range of motion may have been the same as the swollen joints.
5. Patients were to have had an Investigator and parent global assessment at screening of ≥ 10 mm on a 100 mm visual analogue scale (VAS) scale.
6. Patient was to be a candidate for NSAID therapy in Investigator's judgment.
7. If patient was a female of childbearing potential (defined as menarche or ≥ 10 years of age, whichever occurred sooner), she was to have agreed to use adequate contraception (adequate contraception could have included abstinence if the Investigator deemed appropriate) and was to have had a negative urine pregnancy test prior to administration of study medication.
8. Patient's parent or legal guardian was to have provided written informed consent prior to enrollment.
9. Patient, if applicable, was to have assented to participate prior to enrollment.

10. Patient, if applicable, and parent/legal guardian, was to have agreed to comply with study requirements and was to be able to be at the clinic for all required study visits.

JRA Exclusion Criteria

1. Patient will not have in the active phase of systemic JRA, not including isolated chronic anemia, growth failure, or rash;
2. The patient will not have begun taking any of the following medications or will not have changed the dosing regimen of any of these within 12 weeks (or as designated below) before receiving the first dose of study medication:

- Gold salts (including oral gold) – 16 weeks
- Antimalarials
- Sulfasalazine (doses of up to 3 grams/day were allowed)
- Azathioprine
- Penicillamine
- Antibiotics used in treating RA (eg, monocycline or doxycycline)
- Leflunomide (Arava®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Cyclosporine A
- Intravenous (IV) immunoglobulin
- Methotrexate – (>1 mg/kg/week) – 8 weeks
- Anakinra (Kineret™)
- Adalimumab (Humira™)

3. The patient will have begun taking oral corticosteroids or will have changed the dose regimen of oral corticosteroids within 4 weeks prior to Screening (doses of up to 0.2 mg/kg/day or 10 mg prednisone or equivalent/day, whichever was less, will be allowed), or the patient will have received intravenous (IV), intramuscular (IM), intra-articular (IA), or soft-tissue injections of corticosteroids within 4 weeks prior to the Screening visit, (patients will have received a single joint injection after the first 3 month period of the study, if necessary);
4. The patient will have received any cytotoxic medications (other than methotrexate or azathioprine) for JRA during the 12 weeks preceding Screening;
5. The patient will have taken any NSAIDs (including full dose acetylsalicylic acid [ASA] or celecoxib) within 5 half-lives or within 48 hours before receiving the first dose of study medication (Baseline), whichever will be greater. Patients will have discontinued rofecoxib, oxaprozin, an/or piroxicam 4 days prior to the Baseline visit;
6. The patient will not have an active malignancy of any type, or history of a malignancy. Patients with a history of malignancies that had been surgically removed or eradicated by irradiation or chemotherapy and who will have no evidence of recurrence for at least 5 years before study enrollment will be acceptable);
7. The patient will not have been diagnosed as having or will not have received treatment for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before Screening;
8. The patient will not have active GI disease (eg, inflammatory bowel disease), a chronic or acute renal or hepatic disorder, or a significant coagulation defect;
9. The patient will not have received warfarin during the 30 days preceding Screening;

10. The patient will not be taking lithium;
11. The patient will not have an aspartate transaminase (AST), alanine transaminase (ALT) or blood urea nitrogen (BUN) ≥ 1.5 · upper limit of normal (ULN) or creatinine ≥ 1.5 mg/dL or any other laboratory abnormality to be considered by the Investigator to be clinically significant within 14 days before the Baseline visit;
12. The patient will not have a known hypersensitivity to selective COX-2 inhibitors, sulfonamides or NSAIDs;
13. The patient will not have, in the Investigator's opinion, a chronic condition (eg, diabetes, epilepsy) which would be either not stable or well-controlled and could interfere with the conduct of the study;
14. The patient will not have received any investigational medication, including monoclonal antibodies or biologics, other than those explicitly listed above, within 12 weeks before Screening, or will not have received any other immunosuppressant medication, such as tacrolimus or mycophenylate mofetil, within 12 weeks before Screening;
15. The patient will not have used caffeine equivalent to 2 or more cups of coffee per day (7 or more caffeinated soft drinks) per day or alcohol within 24 hours before each visit (Weeks 2, 4, 8, and 12) where a PK sample would be drawn;
16. The patient will not have previously been admitted to this study.
17. Patients receiving methotrexate will not require a dose of >1 mg/kg/week (maximum allowable weekly dose was 40 mg). Patients must have received a stable dose for >8 weeks prior to Screening.

Adult Patients with Rheumatoid Arthritis Eligibility Criterion

Adult Inclusion Criteria
Adult RA patients will have met all of the following inclusion criteria at Baseline (unless otherwise specified) to be eligible for enrollment into the study:
1. Patients were to have a diagnosis of RA by ACR criteria;
2. Patients were to be at least 18 years of age.
3. Patient was to be a candidate for NSAID therapy in the Investigator's judgment.
4. A female patient of childbearing potential was to have agreed to use adequate contraception and was to have had a negative serum pregnancy test prior to the administration of study medication.
5. Patients were to have provided written informed consent prior to enrollment.

Adult Exclusion Criteria
1. The patient will not have a history of any chronic disease other than RA, which in the Investigator's opinion would preclude participation in the study;
2. The patient will not have a history of any clinically significant illness within 30 days before Screening;
3. The patient will not have a history of a) active GI disease (including peptic ulcer); b) chronic or acute cardiovascular, renal, hepatic, or pancreatic disorders which, in the opinion of the Investigator, would be unstable or otherwise precluded participation;
4. The patient will not have a history of substance abuse, drug addiction, or alcoholism;

5. The patient will not have a laboratory abnormality which, in the opinion of the Investigator, would contraindicate study participation, including AST or ALT >1.5 · ULN or creatinine ≥ 1.5 mg/dL;
6. The patient will not any use of an NSAID or salicylate compound within 5 half-lives or within 48 hours before receiving the first dose of study medication, whichever was greater. Patients will have discontinued rofecoxib, oxaprozin, and piroxicam 4 days prior to the Baseline visit.
7. The patient will not have any use of the following medications within 12 weeks or as designated below:

- Gold salts
- Antimalarials
- Sulfasalazine
- Azathioprine
- Penicillamine
- Etanercept (Enbrel®)
- Leflunomide (Arava®)
- methotrexate exceeding 25 mg/week – 8 weeks
- infliximab (Remicade®)
- Cyclosporine A
- tacrolimus
- Anti CD4s, monoclonal antibodies (Mabs), or other biologics
- Prosorba - 1 year
- IM, IA, or soft tissue injections of corticosteroids - 4 weeks.
- anakinra (Kineret™)
- adalimumab (Humira™)

8. The patient will not have caffeine equivalent to 2 or more cups of coffee per day or alcohol consumed within 24 hours prior to a PK sample.
9. The patient will not have had any investigational medication listed above, will not have taken within 12 weeks prior to Screening or will not be scheduled to receive an investigational drug other than celecoxib during the course of the study.
10. Patients will not have a known hypersensitivity to NSAIDs, selective COX-2 inhibitors, or sulfonamides.
11. Patients will not have previously been admitted to the study.
12. The patient will not have begun taking oral corticosteroids or will not have changed the dose regimen of oral corticosteroids within 12 weeks prior to Screening (doses of ≤ 10 mg prednisone or equivalent/day allowed). Patients will not have received IV, IM, IA, or soft-tissue injections of corticosteroids within 4 weeks before Screening.
13. Patients will not be receiving methotrexate in a required dose exceeding 25 mg/week. Patients will have received a stable dose ≥ 8 weeks before Screening and during the study.

Selection of Pediatric and Adult Patients, Sample Size and Power Calculations; Statistical Analysis and Interim Analysis

Approximately 225 patients with JRA will be included in the pivotal efficacy and safety study (Study 195). The subgroups analyzed are shown in Table 66. The sample size was to be based

on the assumption that the percent of patients improved according to the JRA DOI 30 outcome in the naproxen active comparator group would be 60% and that the expected difference between the two treatment groups (celecoxib – naproxen) would be -2%. Therefore, a sample size of 75 pediatric patients per treatment group would give 81% power to conclude non-inferiority. According to the sponsor, results of simulations suggested that a sample size do 75 JRA patients per treatment group and 40 adult patients with RA on celecoxib treatment was sufficient to detect a 30% difference in apparent clearance in JRA patients relative to the adult patients with RA.

Table 66. Study 195, Subgroups Defined by Criteria and Corresponding Variables

Pre-specified Criteria	Variable
Protocol	US or non-US sites (Study 195) Double-Blind Phase Open-Label Phase
Joint involvement	Pauicarticular, Polyarticular, and Systemic course JRA (without active systemic features)
Age group	2-4 yrs., 5-7 yrs., 8-12 yrs., 13-16 yrs
Gender	Female, Male
Race	White, Black, Asian
Height; Weight	Centimeters; Kilograms
Duration of JRA	Years
Onset with Systemic Features	Years
Course of JRA	Pauciarticular, Polyarticular
Baseline (DMARD) user	Yes; No
Baseline DMARD user	Specific name of DMARD
Baseline (BRM) user	Specific name of BRM
Baseline low-dose corticosteroid user	Yes; No
Abbreviations: DMARD = Disease Modifying Anti-rheumatic Drug; BRM = Biologic Response Modifier; yrs. = years; US = United States; Parameters were reported at Baseline by treatment group, celecoxib 3 mg/kg BID; celecoxib 6 mg/kg BID and Naproxen 7.5 mg/kg BID.	

All statistical analyses were to be performed on the intent-to-treat (ITT) cohort. A patient with JRA was to be included in the ITT cohort if he or she would have been randomized to treatment and took at lest one dose of study medication. The primary efficacy endpoint was to be improvement according to the JRA DOI 30 criterion, defined as ≥ 30% improvement in ≥ three core set variables and at most one worsening by > 30%. Change from Baseline at each visit was to be analyzed for the variables listed in the **Secondary Efficacy Endpoints** section of Appendix 10.1. These analyses were to be carried out using an analysis of covariance (ANCOVA) model with treatment group as factor and Baseline values were to be a covariate. All the efficacy and safety analyses were to be performed on the ITT cohort. If a patient were to not have a post baseline assessment, then the Baseline value was to be carried forward for all efficacy variables. For all other patients, the last observation carried forward (LOCF) method would be used to impute missing values.

Pursuant to agreement with the FDA, Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, and as was specified in the Pediatric Written Request (WR), the non-inferiority

hypothesis testing was to be one-sided at the 2.5% level of significance, or equivalently, non-inferiority of a celecoxib dose was to be claimed if the lower limit of the 95% 2-sided confidence interval for the difference in the proportion of JRA DOI 30 responders was above -25%. This hypothesis was to be tested for each of the two doses of celecoxib versus naproxen, separately. Rejection of null hypothesis fro at least one of the celecoxib doses at Week 12 was to be sufficient to conclude non-inferiority of celecoxib at that dose level to naproxen in treating signs and symptoms of JRA. All other comparisons were 2-sided at the 5% level of significance. Type I error was not to be controlled for multiple comparisons or for multiple endpoints.

According to the sponsor, following the voluntary worldwide withdrawal of VIOXX (rofecoxib) by Merck and at the request of FDA, a Data Safety Monitoring Board (DSMB) was chartered and conducted two early unblinded assessments of the available data. The first unblinded assessment of was only of those patients who had experienced a serious adverse event (SAE). The second assessment was performed when all the pediatric patients had completed the double-blind phase of Study 195; but, before the study was officially unblinded. (See the Safety Analyses section of this protocol.) At this juncture, there were still pediatric patients ongoing in the open-label phase (Study 195). The sponsor explained that access to unblinded information was restricted to the DSMB and a limited number of personnel at Pfizer operationally responsible for assembling study results for the DSMB.

Efficacy Variables

Primary Endpoint

The proportion of patients with JRA meeting the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) was selected as the primary efficacy endpoint based on regulatory guidance. The JRA DOI 30 was developed by a consensus process of pediatric rheumatologists conducted similarly to the development of the ACR20 (American College of Rheumatology 20) endpoint used in adult patients with RA. A clinically meaningful improvement using the JRA DOI 30 of at least 30% improvement in any of three of the six core variables, with no more than one of the remaining variables not worsened by more than 30%. The core set of the six variables for the JRA DOI 30 are as follows:

1. Physician Global Assessment of Disease Activity (measured on a 100-mm visual analogue scale [VAS], between 0 (no disease activity) and 100 (most severe disease activity);
2. Parent's Global Assessment of Overall Well-Being (Childhood Health Assessment Questionnaire [CHAQ] subsection). The parent/legal guardian was asked to rate their child's overall well-being by placing one vertical line on a 100-mm VAS between 0 (very well) and 100 (very poor).
3. Parent's Assessment of Physical Function (CHAQ Disability Index).
4. Number of joints with active arthritis (defined as the presence of swelling not due to currently inactive synovitis or to bony enlargement or, if no swelling was present, limitation of motion accompanied by heat, pain or tenderness);
5. Number of joints with limited range of motion; and
6. Laboratory marker of inflammation (C-reactive protein [CRP]).

Secondary Endpoints

Change from Baseline at each visit was to be analyzed for the following:

1. Physician Global Assessment of Disease Activity;
2. Parent's Global Assessment of Overall Well-Being (CHAQ subsection);
3. Parent's Assessment of Physical Function (CHAQ Disability Index);
4. Parent's Assessment of Child's Arthritis Pain (VAS) [CHAQ subsection];
5. Number of joints with active arthritis;
6. Number of swollen and tender/painful joints assessed separately;
7. Number of joints with limited range of motion;
8. CRP
9. Peds QL.

Other Endpoint Evaluations

1. Parent's Assessment of Child's Arthritis Pain (VAS) [CHAQ subsection];
2. Pediatric Quality of Life Inventory (PedsQL ^{TM})

Exploratory Endpoints

1. Post hoc exploratory analyses were to be performed separately for the percentage of patients with either pauciarticular course JRA or polyarticular course JRA for the JRA DOI 30 criterion.
2. Post-hoc analyses were to be performed separately for the percentage of patients who met either the JRA DOI 50 criterion or the JRA DOI 70 criterion.

Compliance

The volume of suspension remaining in bottles A and B was to be measured and recorded on the "Site Drug Inventory and Dispensing Record for the Individual Patient in Double-blind Period" form at Weeks 2, 4, and 8. See Table 67. The volume of suspension which would be remaining in the bottle at Week 12 (or Early Termination of the double-blind phase), Weeks 16, and 24 (or Early Termination of the open-label phase) was to be measured and recorded on the "Site Drug Inventory an Dispensing Record for Individual Subject in Open-Label Period" form.

Table 67. Clinical Supplies for JRA Patients: Double-Blind Phase (Study 195)
(From sponsor Table 9, page 46 of 4701)

Bottle	Contents
A	Celecoxib 50 mg/5 mL (low dose) oral suspension or celecoxib 100 mg/5 mL (high dose) oral suspension, or placebo for celecoxib oral suspension; (473 mL)
B	Naproxen 125 mg/5 mL oral suspension or placebo for naproxen oral suspension; (473 mL)

Analysis of Safety

Safety was assessed by physical examinations, medical history, vital signs, weight, height, clinical laboratory parameters, developmental evaluation (as part of the medical history and physical examination), slit lamp examination by an ophthalmologist, and reporting of adverse events. A disseminated intravascular coagulation (DIC) panel for any patient who experienced a flare of systemic features was to be performed. All randomized patients (adult patients with RA and patients with JRA) who would have received at least one dose of study medication were to be included in the analysis of safety. The degree of severity of an event was to be reported. The

open-label adverse event data was to be summarized from the open-label Baseline visit to Week 24, the Final visit.

Protocol Amendments
Study 195 was amended eight times. As per the sponsor's explanation, Amendments 1, 2, 4, 7 and 8 were amendments that applied to all study centers. Amendments 3 and 5 were country specific amendments, and Amendment 6 was a center specific amendment relevant to the adult RA cohort.

Amendment 1, dated 12 August 2002, was designed to:
- Update the clinical monitor;
- Revise the joints that will be assessed/not assessed for limited range of motion and/or swelling;
- Correct errors to the JRA and adult schedule of events and clarify the schedule for collection of PK samples;
- Remove the request that arthritis assessments occur at approximately the same time of day as the Baseline visit, which was not possible due to the PK sample collection schedule;
- Clarify the collection procedure, schedule, storage and shipment of PK samples.

Amendment 2, dated 11 September 2002, was designed to:
- Correct typographical errors;
- Correct the PK sampling time for adult subjects;
- Clarify the number of mLs of suspension to be administered to adult subjects;
- Correct the total volume of blood collected for PK samples;
- Clarify the visit at which the pre-dose PK sample was collected on the adult cohort.

Amendment 3, dated 28 May 2003, a country-specific amendment relevant only to Norway was designed to:
- Remove the sections of the protocol pertinent to the open-label phase of the study. Norway elected not to participate in this phase of the study.

Amendment 4, dated 17 October 2003, was designed to:
- Remove the Baseline clinical laboratory tests for JRA subjects to minimize the number of blood draws to the pediatric cohort;
- Include a CRP at Screening and remove it from the Baseline visit, to minimize the number of blood draws to the pediatric cohort;
- Include a urine pregnancy test at the Week 2 visit to enhance the safety of females of childbearing potential and unborn children;
- Add a DIC panel (fibrinogen, FDP, and D-dimer) for those subjects potentially experiencing a flare of systemic features of JRA during the trial;
- Remove the Parent's Assessment of Physical Function from the Screening visit;
- Revise the JRA inclusion/exclusion criteria as follows:
- Reduce the minimum weight criterion from 15 kg to 9 kg to facilitate enrollment of younger children;

- Remove the CHAQ inclusion criterion;
- Reduce the Physician's Global Assessment of Disease Activity inclusion criterion from a score of ≥ 20 mm to ≥ 10 mm on a 100-mm VAS;
- Reduce the Parent's Global Assessment of Overall Well-Being inclusion criterion from a score of ≥ 20 mm to ≥ 10 mm on a 100-mm VAS;
- Increase the allowable methotrexate dose to 1 mg/kg/day (up to a maximum allowable dose of 40 mg/week), consistent with current clinical practice;
- Allow anakinra (Kineret™) and adalimumab (Humira™) as standard of care therapy provided the subject had been on a stable dose for 12 weeks prior to entry;
- Revise the adult inclusion criteria to allow prednisone up to 10 mg per day;
- Include flare of systemic features of JRA as a criterion for withdrawal of subjects from the trial;
- Revise the dosing scheme for JRA subjects. Subjects were previously assigned to low weight (15-25 kg), 2.5 mL BID; medium weight (26-50 kg), 5 mL BID; and high weight (>50 kg), 10 mL BID for Bottle A, and 20 mL BID for Bottle B. The dosing scheme was revised to the following doses for the following weight categories: 9-14 kg (2.5 mL BID), 15-25 kg (5 mL), 26-38 kg (7.5 mL BID), 39-50 kg (10 mL BID), and >50 kg (15 mL BID for Bottle A and 20 mL BID for Bottle B).

Amendment 5, an amendment specific to Norway, dated 31 October 2003, was designed to:

- Remove the sections of the protocol pertinent to the open-label phase of the study, revised within **Amendment 4.** Norway elected not to participate in this phase of the study.

Amendment 6, a center-specific amendment relevant only to the adult cohort, dated 09 February 2004, was designed to:

- Revise the adult inclusion/exclusion criteria as follows:
- Allow stable, chronic disease which would not interfere with the subject's participation in the study;
- Revise allowable methotrexate dose from <25 to ≤25 mg/week;
- Allow tobacco use.

Amendment 7, dated 06 July 2004, was designed to:

- Provide a complete and current list of the countries participating in the trial;
- Provide a complete definition of a joint with active arthritis;
- Clarify that the developmental assessment was expected at each physical examination (previously included in the CRF instructions with a worksheet to be completed by the site);
- Remove lactose intolerance as an exclusion criterion for the JRA subjects as lactose is not an ingredient in the suspension;
- Remove tobacco use as an exclusion criterion for the JRA subjects as nicotine does not induce 2C9 and thus has no effect on celecoxib metabolism;

- Revise the dosing scheme for JRA subjects to the following: 9-12 kg (2.5 mL BID), 13-25 kg (5 mL), 26-37 kg (7.5 mL BID), 38-50 kg (10 mL BID), and >50 kg (15 mL BID for Bottle A and 20 mL BID for Bottle B);
- Revise the number of bottles to be dispensed to the JRA subjects at each visit during the open-label phase;
- Revise the safety reporting section to amend the reporting period for serious adverse events to the time of informed consent and to provide more detailed guidelines for the definition and reporting of all adverse events;
- To clarify that plasma samples were assayed on an ongoing basis throughout the trial in order not to exceed the established timeframes of analytical integrity of the samples;
- To revise contact information for serious adverse events.

Amendment 8, dated 18 Jan 2005, was designed to:

- Form a DSMB at the request of the FDA to ensure the safety of pediatric subjects participating in the open-label phase of the trial.

The following are clarifications and additions to the statistical methods that were described by the SAP.

- At the request of the FDA, a comprehensive early assessment of safety data was performed by a DSMB when all subjects had completed the double-blind phase of the study, but before the study was officially unblinded.
- To be consistent with previous celecoxib studies, post hoc analyses were performed on the incidence of withdrawals and time to withdrawal due to LOE for subjects who withdrew due to LOE during the double-blind phase. The incidence of withdrawals due to LOE was compared using Fisher's exact test. Time to withdrawal was examined using the log-rank test. Kaplan-Meier plots were also displayed.
- Clarifications to the double-blind efficacy windows described in the SAP are as follows and are reflected in the programming. Double-blind Baseline is defined as the last observation on or prior to the date of first dose of double-blind medication. The other week intervals, based on study days are as follows: 2 to 19 for Week 2, 20 to 33 for Week 4, 34 to 63 for Week 8, 64 to 93 for Week 12, with the Week 12 observation happening no more than 9 days after the last dose of double-blind study medication and occurring on or before the date of first dose of open-label study medication, if applicable.
- Post hoc analyses were performed separately for systolic and diastolic BP (sitting). ANCOVA models were employed on the change from Baseline to Week 12/End of double-blind with factors for treatment, Baseline values, gender, age, and height as covariates. Additionally, post hoc analyses were performed on height and weight. ANCOVA models were employed on the change from Baseline to Week 12/End of double-blind with factors for treatment, Baseline values of height and weight, gender, and age as covariates. Additionally, comparison of extreme weight values by age was performed from double-blind Baseline to Week 12/end of double-blind. Treatment groups were compared using Fisher's exact test.
- Clarifications were made to the Baseline definitions for summarization of the open-label treatment phase and are described in Section 5.10.4.2 of the NDA submission, Open-Label Treatment Phase. Unblinding occurred for 2 subjects during the study. Patient

1211 experienced a severe allergic reaction, and Subject 1351 experienced acute cytomegalovirus (CMV). In both instances, the Investigator contacted IVRS to determine the subject's treatment assignment.

Protocol Violations are reported in Section 6.1 Efficacy of this review.

Clinical Pharmacokinetic Studies
See Section 5.0, Clinical Pharmacology, of this NDA review for this Medical Officer's comments about the PK studies submitted in Supplement 021. The following PK study results are analyzed in the Clinical Pharmacology review by Srikanth Nallani, PhD.

Study A3191202 (Study 1202)
"A Relative Bioavailability Study of Celecoxib Administered as Capsule Contents Sprinkled on Applesauce in Healthy Adult Volunteers"

Study N49-98-02-088 (Study 088)
An 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"

Study A3191162 (Study 1162)
"An Open-Label, Randomized, Four-Period, Four-Treatment, Relative Bioavailability Study of Celecoxib Commercial Capsule and Suspension Formulations in Healthy Volunteers"

Study RR 754-00049 (RR 049)
"Population Pharmacokinetics of Celecoxib in Pediatric Patients with Juvenile Rheumatoid Arthritis"

10.2 Line-by-Line Labeling Review

TBD.

REFERENCES

References noted are listed within the specific section of the review.

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/s/

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12/5/2006 06:17:45 PM
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MO Rev Celecoxib JRA Supplement

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