CLINICAL REVIEW

Application Type	NDA 21-042/S-026 NDA 21-052/S-019
Submission Code	SE5
Letter Date	December 5, 2003
Stamp Date	December 5, 2003
Received	January 6, 2004
Reviewer Name	Carolyn L. Yancey, MD, Medical Officer
Completion Date	June 4, 2004
Established Name	Rofecoxib
Trade Name	VIOXX
Therapeutic Class	NSAID (Selective COX-2-Inhibitor)
Applicant	Merck Research Laboratories
Priority Designation	P Pediatric Exclusivity
Formulation	Tablet and Suspension
Dosing Regimen	Oral tablets: 12.5, 25 mg Oral suspension: 12.5mg/5 ml; 25 mg/5 ml
Proposed Indications	Signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)
Intended Population	Poly- and pauciarticular JRA
Related Reviews	Clinical Pharmacology, Lei Zhang, PhD and Jenny J. Zheng, PhD; Statistics, Atiar M. Rhaman, PHD; NDA 21-042 (capsules) and NDA 21-052 (oral solution) S007 Gastrointestinal Safety
Project Manager	Barbara Gould

Table of Contents

1 EXECUTIVE SUMMARY 4

1.1.1 RECOMMENDATION ON APPROVABILITY 4
1.1.2 RECOMMENDATION ON POST-MARKETING ACTIONS 4
1.1.3 Risk Management Activity 4
1.1.4 Required Phase 4 Commitments 4
1.1.5 Other Phase 4 Requests 5
1.1.6 SUMMARY OF CLINICAL FINDINGS 5
1.1.7 Brief Overview of Clinical Program 5
1.1.8 Efficacy 7
1.1.9 Safety 8
1.1.10 Dosing Regimen and Administration 10
1.1.11 Drug-Drug Interactions 11
1.1.12 Special Populations 11

2 INTRODUCTION AND BACKGROUND 11

2.1.1 PRODUCT INFORMATION 11
2.1.2 STATE OF ARMAMENTARIUM FOR INDICATION(S) 12
2.1.3 AVAILABILITY OF PROPOSED PRODUCT IN THE U.S. 12
2.1.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 12
2.1.5 PRE-SUBMISSION REGULATORY ACTIVITY 13
2.1.6 OTHER RELEVANT BACKGROUND INFORMATION 14

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 14

3.1.1 CHEMISTRY (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 15

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 15

4.1.1 SOURCES OF CLINICAL DATA 15
4.1.2 TABLES OF CLINICAL STUDIES 15
4.1.3 REVIEW STRATEGY 16
4.1.4 DATA QUALITY AND INTEGRITY 16
4.1.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 17
4.1.6 FINANCIAL DISCLOSURES 17

5 CLINICAL PHARMACOLOGY 17

5.1.1 PHARMACOKINETICS (PK) SEE CLINICAL PHARMACOLOGY REVIEW BY LEI K. ZHANG, PHD AND JENNY J. ZHENG, PHD. 17
5.1.2 PHARMACODYNAMICS 18
5.1.3 EXPOSURE-RESPONSE RELATIONSHIPS 18

6 INTEGRATED REVIEW OF EFFICACY 18

6.1.1 METHODS 18
6.1.2 GENERAL DISCUSSION OF ENDPOINTS 19
6.1.3 EFFICACY FINDING AND RESULTS 20
6.1.4 ASSUMING MISSING VALUE AS MISSING 39
6.1.5 ASSUMING MISSING VALUE AS FAILURE 39
6.1.6 CLINICAL MICROBIOLOGY 43
6.1.7 EFFICACY CONCLUSIONS 43

7 INTEGRATED REVIEW OF SAFETY 44

7.1.1 METHODS AND FINDINGS 44
7.1.2 Human Reproduction and Pregnancy Data 64
7.1.3 Overdose Experience 65

7.1.4 Post-marketing Experience *65*
7.1.5 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 65
7.1.6 Adequacy of Special Animal and/or In vitro Testing *65*
7.1.7 Adequacy of Routine Clinical Testing *65*
7.1.8 Adequacy of Metabolic, Clearance, and Interaction Workup *65*
7.1.9 Assessment of Quality and Completeness of Data *65*
7.1.10 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS 66
7.1.11 SAFETY CONCLUSIONS 66

8 ADDITIONAL CLINICAL ISSUES 66

8.1.1 DOSING REGIMEN AND ADMINISTRATION 66
8.1.2 DRUG-DRUG INTERACTIONS 66
8.1.3 SPECIAL POPULATIONS 67
8.1.4 PEDIATRICS 67
8.1.5 ADVISORY COMMITTEE MEETING 67
8.1.6 LITERATURE REVIEW 67
8.1.7 OTHER RELEVANT MATERIALS 67

9 OVERALL ASSESSMENT 68

9.1 CONCLUSIONS ON AVAILABLE DATA 68
9.2 RECOMMENDATION ON REGULATORY ACTION 68
9.3 RECOMMENDATION ON POST-MARKETING ACTIONS 69
9.3.1 Risk Management Activity *69*
9.3.2 Required Phase 4 Commitments *69*
9.3.3 Other Phase 4 Requests *69*
9.4 LABELING REVIEW 69

10 APPENDIX 69

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 69
10.2 LINE-BY-LINE LABELING REVIEW 89

1 EXECUTIVE SUMMARY

This Executive Summary is restricted to the evaluation of NDA 21-042, Supplement 026 (tablets), and the NDA 21-052, Supplement 019 (suspension), for the efficacy and safety of VIOXX (rofecoxib) for the proposed indication of treatment of the signs and symptoms of pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years to 17 years of age. VIOXX was approved for adult treatment May 20, 1999. The Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products (DAAODP), HFD-550, issued a pediatric Written Request (WR) on May 7, 2001 pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Merck Research Laboratories (MRL) to obtain needed pediatric information about VIOXX (rofecoxib) tablets and suspension. MRL responded to the pediatric WR on December 5, 2003 with submissions, NDA 21-042/S-026 and NDA 21-052/S-019, consisting of six studies, including the tablet and suspension formulations: four pharmacokinetic (PK) studies, one Phase 3 clinical efficacy and safety study and one open-label extension study in JRA patients. The Food and Drug Administration (FDA) granted MRL six months of marketing exclusivity for VIOXX (rofecoxib) on February 18, 2004 based on the submitted pediatric supplements cited above, study of tablet and oral suspension, performed to investigate the use of VIOXX for treatment of JRA.

1.1.1 Recommendation on Approvability

Approval is recommended for rofecoxib, oral suspension and tablets, (b) (4) 0.6mg/kg/day to a maximum dose of 25mg once per day, indicated for relief of the signs and symptoms of pauciarticular and polyarticular course JRA in patients ≥ 2 years to ≤ 17 years of age. The effect size and the adverse event profile (b) (4) demonstrate statistical non-inferiority to naproxen with an acceptable adverse event profile. (b) (4)

The Division recommends label changes in the following sections of the current approved VIOXX (Rofecoxib) label: See separate document for text in the following sections. CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, INDICATIONS and ADVERSE REACTIONS

1.1.2 Recommendation on Post-Marketing Actions

1.1.3 Risk Management Activity

The sponsor should continue to report post-marketing data collected in the Worldwide Product Safety Report Generation System to the DAAODP, HFD-550. There is no additional recommended JRA patient risk management activity.

1.1.4 Required Phase 4 Commitments

There are no required Phase 4 commitments.

1.1.5 Other Phase 4 Requests

There were no clinical or PK studies of rofecoxib oral suspension in JRA patients weighing less than 10 kg submitted in these pediatric supplements. In consideration of the small number of JRA patients, recruitment for Phase 4 studies with rofecoxib suspension to further define PK exposure, dosage and safety for JRA patients with body weight less than 10 kg will be difficult.

1.1.6 Summary of Clinical Findings

Within the non-inferiority study design of these two clinical trials, utilizing an active comparator arm, the primary endpoint for evaluating efficacy was the proportion of patients meeting the JRA Definition of Improvement ≥ 30% (JRA DOI 30), a composite score of 6 core variables. The proportion of patients meeting the JRA DOI 30 criterion, regardless of completion status, over the 12-week study was (b) (4) 54.5% and 55.1% in (b) (4) higher-dose rofecoxib and naproxen treatment groups, respectively. From the 12-week study, rofecoxib, as 0.6 mg/kg per day to a maximum of 25mg per day, is an acceptable dose for treatment of pauciarticular or polyarticular JRA in patients ≥ 2 years and ≤ 17 years of age. Higher-dose of rofecoxib appears to offer acceptable durability, using the JRA DOI 30 criterion.

The overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of rofecoxib and naproxen. Caution should be used when administering rofecoxib to JRA patients taking concomitant mediations with similar adverse event profiles as rofecoxib.

1.1.7 Brief Overview of Clinical Program

VIOXX (Rofecoxib) tablet (12.5mg; 25mg) and suspension (12.5mg/5ml; 25mg/5ml) [both formulations are bioequivalent] is a selective cyclogenase-2 (COX-2) inhibitor which inhibits prostaglandin synthesis. Rofecoxib is indicated for the treatment of osteoarthritis, rheumatoid arthritis, (b) (4) acute pain, and dysmenorrhea in the United States (b) (4) In these two pediatric supplements, rofecoxib was studied for the indication of relief of signs and symptoms of pauciarticular and polyarticular course JRA in patients ≥ 2 years to ≤ 17 years old.

Overall number of patients enrolled and exposed:

Note the word "patients" in the below protocol descriptions of enrollment and exposure refers to "patients with pauciarticular and polyarticular course JRA". The words "adults with RA" in Protocol 228 description below refers to "adult patients with Rheumatoid Arthritis" (RA). See Section 4.1 Data Sources, Review Strategy and Data Integrity, Sub-Section 4.2 Tables of Clinical Studies for additional study details.

Protocol 134/135 Clinical Efficacy, Safety

Enrolled 310 patients: 285 patients completed the study, 99 patients were treated with rofecoxib 0.3mg/kg/day, 95 patients were treated with rofecoxib 0.6mg/kg/day and 91 patients were treated with naproxen 15mg/kg/day.

Protocol 134/135 Open-Label Extension

Enrolled 227 patients: 181 patients completed the study, 134 patients were treated with rofecoxib 0.6mg/kg/day and 47 patients were treated with naproxen 15mg/kg/day.

Protocol 105

Enrolled 11 patients: 7 patients were treated with rofecoxib 12.5mg/day and 4 patients were treated with rofecoxib 25mg/day.

Protocol 109

Enrolled 26 patients: 25 patients received study medication, 10 patients were treated with rofecoxib 5mg/day, 8 patients were treated with rofecoxib 7.5mg/day and 7 patients were treated with rofecoxib 10mg/day.

Protocol 110

Enrolled 12 patients: 10 patients completed this study and all 10 were treated with rofecoxib 0.7mg/kg/day.

Protocol 228

Enrolled 14 adults with RA: 12 completed the study with rofecoxib 25mg/day.

One Phase 3, 12-week study of efficacy and safety with an open-label extension, **Protocol 134/135***, was designed to assess both the short-term and long-term efficacy and safety of the treatment effect of rofecoxib in patients with JRA. The 12-week portion was a double-blinded, double-dummy, active-controlled trial to evaluate the efficacy and safety of rofecoxib for treatment of JRA was designed to investigate whether the proportion of patients that demonstrate improvement, defined by the JRA DOI 30 criterion, was similar between the rofecoxib and naproxen treatment groups. The 52-week, open-label, active-controlled extension to the 12-week trial of rofecoxib in JRA patients was designed to investigate the durability and effect, tolerability and safety of chronic administration of rofecoxib. Ethical considerations precluded performing a placebo-controlled study in a JRA population with a chronic, painful inflammatory disease. Naproxen, approved for treatment of JRA, was used as the active comparator.

In the 12-week study, the mean duration of exposure in 2 year to 11 year old patients was 81.6, 82.3 and 80.6 days for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. The mean duration of exposure in 12 year to 17 year old patients was 82.2, 84.7 and 79.2 days for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen groups, respectively.

Four PK studies were completed. **Protocol 105** was an open-label study to evaluate the steady-state plasma concentration profile of rofecoxib in late-stage and post-pubertal adolescents, 12 to 17 years of age with JRA. This study was followed by a 12-week, double-blind, active-controlled extension. The PK portion of this study was designed to investigate area under the curve (AUC) of rofecoxib at steady state in adolescent JRA patients compared to rofecoxib 25mg daily adult historical controls. Similarly, **Protocol 109 and Protocol 110,** investigated the same PK parameters and adult comparisons as in Protocol 105 except the JRA patients were 2 years to 11 years and 2 years to 5 years, respectively. **Protocol 228** was a single-period, multiple-dose PK study in adult RA patients to investigate the steady-state plasma concentration profile of rofecoxib.

Safety and efficacy data were assessed in the 6 completed trials, though the four PK trials included small numbers of JRA patients and did ***not*** include either an active comparator or placebo. Therefore, the safety database includes 310 patients from the 12-week base study, Protocol 134/135, and 227 patients from the 52-week open-label extension portion of this study.

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-550. Electronic post-marketing data submitted by the sponsor was reviewed but was not summarized in this review.

** Note: **Protocol 134/135** was a multicenter (41) study: Australia, Europe, Mexico, Israel, South America, United States; **Protocols 134 and 135** were **identical**. The protocols were assigned different numbers to differentiate the **domestic study**, **Protocol 134** from the **multinational study**, **Protocol 135**. This was a 12-week, double-blind, double-dummy, active comparator-controlled study in 2 to 17 year old pauciarticular and polyarticular JRA patients. The use of 2 protocol numbers was administrative to allow compliance with regulatory requirements in different regions. The study was designed as a single study. Throughout this review, Protocol 134/135 numbers will be used together and the specific trial under review will be clearly explained. Only higher-dose rofecoxib was used in the open-label extension study.*

1.1.8 Efficacy

12-Week Study, Protocol 134/135: There were 310 JRA patients in this double-blind, non-inferiority trial. Two study doses of rofecoxib were compared to naproxen. Rofecoxib was administered as a lower-dose of 0.3mg/kg per day to a maximum of 12.5mg per day and as a higher-dose of 0.6mg/kg per day to a maximum of 25 mg per day. The active comparator, naproxen, was administered as approximately 7.5mg/kg per day, twice daily.

The prespecified criterion for the non-inferiority trial design was the lower limit margin of the point estimate, of the 95 % confidence interval (CI) for the ratio of the JRA Definition of Improvement (JRA DOI 30) responder rate (rofecoxib/ naproxen) (b) (4) Patients are classified as improved if they experience ≥ 30% improvement in at least three of 6 of the JRA DOI core set variables, with no more than one of the 6 variables worsening by more than 30%.

(b) (4) This review was conducted using a lower limit margin of ≥ 0.75, employing this margin, as discussed below (b) (4)

The point estimate was 0.98 (95% CI, **0.76*** to 1.26), in a modified intent-to-treat analysis (MITT), using the JRA DOI 30 responder index, *regardless of completion status* and the point estimate was 1.00 (95% CI, **0.78*** to 1.29), MITT, by the JRA DOI 30 *responder and completer status.* (b) (4)

[redacted] (b) (4)

The proportion of patients who achieved the JRA DOI 30 criterion, MITT, *regardless of completion status*, over the 12-week study was [redacted] (b) (4) 54.5% and 55.1% for the [redacted] (b) (4) higher-dose rofecoxib and naproxen treatment groups, respectively.

Secondary endpoints: The proportion of patients with improvement from baseline in the parent/patient's assessment of overall well-being, parent/patient assessment of pain and discontinuation the study dose due to lack of efficacy was similar across the three treatment groups with no statistically significant differences between the treatment groups. In the assessment of the individual components of the JRA DOI 30, naproxen demonstrated statistically significant improvement in the number of joints with limited range of motion, compared to both higher-dose and lower-dose rofecoxib. No other component of the JRA DOI 30 had a statistically significant difference across the three treatment groups.

52-Week Open-Label Extension, Protocol 134/135: The proportion of patients achieving the JRA DOI 30 criteria, *regardless of completion status,* was 66.7% and 60.3%; and, for *responders and completing,* was 57.9% and 42.4%, for rofecoxib and naproxen, respectively.

In conclusion from the 12-week study, rofecoxib, as 0.6 mg/kg per day to a maximum of 25mg per day, is an effective dose for treatment of pauciarticular or polyarticular JRA in patients ≥ 2 years and ≤ 17 years of age. The higher-dose of rofecoxib appears to offer durability over the 52-week extension study period.

1.1.9 Safety

During the **12-week, double-blind portion of this study, Protocol 134/135,** safety data was collected from 310 JRA patients, 109 and 100 patients, treated with lower-dose rofecoxib and higher-dose rofecoxib, respectively. One-hundred-and-one JRA patients were treated with the active comparator, naproxen. The **52-week open-label extension** collected safety data from 160 and 67 JRA patients, rofecoxib and naproxen, respectively. In this open-label extension, only the higher-dose rofecoxib was studied.

Deaths
There were no deaths, malignancies, significant overdoses or pregnancies in the 12-week study or in the 52-week open-label extension.

Serious Adverse Events
In the 12-week study, there were four **serious adverse events** (SAE) reported as JRA flare. Of these four patients, one was treated with lower-dose rofecoxib, two were treated with higher-dose rofecoxib and one was treated with naproxen. In the 52-week

extension, there were SAEs reported in 10 and 7 patients, for rofecoxib and naproxen, respectively. Two of these 17 SAE resulted in discontinuation of study medication, one patient developed hepatitis A (rofecoxib group) and one patient suffered worsening of their JRA (naproxen group).

Discontinuations Due to Adverse Events
In the 12-week study, 5 patients withdrew due to adverse events. Of these five patients, two patients treated with lower-dose rofecoxib suffered abdominal pain; 1 patient treated with lower dose rofecoxib suffered worsening JRA; 1 patient, treated with naproxen, suffered headaches and 1 patient, treated with naproxen, suffered hematochezia.

In the 52-week extension, 12 patients discontinued study medication due to the following clinical adverse events:

- 4 patients discontinued rofecoxib treatment secondary to GI disorders, upper abdominal pain (1 patient) and gastritis (1 patient), alopecia (one patient) and hepatitis A (1 patient).
- 8 patients discontinued naproxen treatment secondary to GI disorders, GI upset, upper abdominal pain, abdominal pain and constipation (5 patients), worsening JRA (2 patients) and hepatitis A (1 patient).

Non-Serious Adverse Events
In the 12-week study, there were 196 non-serious adverse events observed in the three treatment groups. In the 52-week open label extension, there were 171 non-serious adverse events among 227 JRA patients.

In the 12-week double-blind study, **gastrointestinal disorders** as abdominal pain, upper abdominal pain, diarrhea and nausea, **upper respiratory tract infections** and **headache** were the three most commonly reported **adverse events**. There were 29(26.6%), 32(32%) and 40 (39.6%) patients with GI adverse events, the lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. A higher incidence of **abdominal pain** was noted in the naproxen treated group, 13 patients (12.9%), compared to the 7 patients (6.4%), lower-dose of rofecoxib, and 6 patients (6.0%) higher-dose of rofecoxib. **Upper abdominal pain** occurred in 7 patients (6.4%), 12 patients (12.0%) and 7 patients (6.9%) treated with lower-dose rofecoxib, higher-dose rofecoxib, and naproxen. **Upper respiratory tract infections** were the second most common adverse event. Upper respiratory tract infection was noted in 6 patients (5.5%), 6 patients (6.0%) and 7 patients (6.9%) treated with lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. Nasopharyngitis was noted in 11 patients (10.1%), 1 patient (10.0%) and 1 patient (1.0%) and pharyngitis was noted in 7 patients (6.4%), 3 patients (3.0%) and 3 patients (3.0%) treated with lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. **Headache** was the third most commonly reported clinical adverse event occurring in 6 patients (5.5%), 5 patients (5.0%) and 13 patients (12.9%) in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. Headache is a well-known adverse event with naproxen, other NSAIDs and selective COX-2 inhibitors.

Pyrexia occurred in each treatment group with increased incidence in the naproxen treatment group. Insomnia occurred in each treatment group with increased incidence in the higher-dose rofecoxib group. Two cardiorenal system adverse events were reported, one patient treated with higher-dose rofecoxib suffered edema of the feet and ankles and one patient treated with naproxen reported swelling on the dorsum of the foot. Allergic skin/hypersensitivity reactions were noted in each three treatment groups as 9, 11 and 10 patients for lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment, respectively. There was one case of pseudoporphyria reported with higher-dose rofecoxib treatment.

In the 52-week extension, the most common adverse events were **upper respiratory tract infections**, **gastro-intestinal events,** as upper abdominal pain, abdominal pain and diarrhea, **headache** and **pyrexia**.

Laboratory Adverse Events
In the 12-week study, the most common laboratory adverse event was **elevated hepatic enzymes**. Hepatic enzymes were reported as abnormal if consecutive values were 3 x upper limit of normal (ULN). Abnormal hepatic enzymes were reported in five, four and two patients in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. Four patients discontinued study drug due to elevated hepatic enzymes, three patients in the lower-dose rofecoxib group and one patient in the higher-dose rofecoxib group. There were no abnormal bilirubin values. Less common laboratory adverse events of note were abnormal urinalysis, two patients on naproxen treatment, and urinalysis with protein, two patients treated with low-dose rofecoxib and two patients treated with naproxen.

In the 52-week extension, the incidence of adverse laboratory tests, **elevated hepatic enzymes**, ALT and/or AST, was numerically larger in the rofecoxib treatment group than in the active comparator group. One patient treated with rofecoxib was discontinued from study therapy.

In conclusion, the overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of rofecoxib and naproxen. However, caution should be used when administering rofecoxib to JRA patients taking concomitant mediations with similar adverse event profiles as rofecoxib due to the potential for synergistic toxicity. Safety monitoring for clinical signs and symptoms of adverse events is important, particularly, for the risk of hepatotoxicity. Concomitant medication, specifically DMARD therapy, appears to increase the risk of elevation of hepatic enzymes.

1.1.10 Dosing Regimen and Administration

The rofecoxib dose in the 12-week study and the 52-week open-label extension, Protocol 134/135, was based on results of PK studies with JRA patients. The recommended dose, based upon the review of the two NDA pediatric supplement data, is 0.6mg/kg per day up to a maximum dose of 25 mg per day in JRA patients ≥ 2 years and ≤ 17 years of age.

This dose is supported by the non-inferiority trial design findings from the efficacy measurements and supported by the safety profile in both the 12-week study and the 52-week extension.

1.1.11 Drug-Drug Interactions

Pediatric patients with hypersensitivity (e.g., angioedmea and/or bronchoconstriction) to aspirin and/or nonsteroidal anti-inflammatory drugs were excluded from these rofecoxib clinical trials. Similarly, caution should be used with concomitant medications such as gold, methotrexate, sulfasalzine, anti-malarials and steroids because the adverse event profiles are similar and concomitant medication may precipitate adverse experiences.

1.1.12 Special Populations

The selective COX-2 inhibitor, rofecoxib, has been studied in the adult special populations previously. Clinical studies demonstrate safety risks because renal clearance may be decreased from normal; similarly, hepatic insufficiency may be worsened because of the drug's hepatic metabolism and decreased plasma protein binding in liver disease.

There are three subtypes of JRA characterized by course of onset: pauciarticular, polyarticular and systemic JRA with approximately 60%, 30 % and 10% frequency of cases, respectively. JRA is one of the most common rheumatic disease of childhood and the leading cause of childhood disability, affecting approximately 1.3 to 22.6 per 100,000 pediatric patients in North America. This pediatric program enrolled 144 pauciarticular and 166 polyarticular JRA patients. These supplements did not study pauciarticular *versus* polyarticular JRA differences in response to rofecoxib. Systemic JRA was not included in this review due to known risks and the more common need to adjust doses of concomitant medications in this course of JRA.

2 INTRODUCTION AND BACKGROUND

2.1.1 Product Information

- Rofecoxib is a selective COX-2 inhibitor with a mechanism of action believed to be due to inhibition of prostanglandin synthesis via inhibition of cyclooxygenase-2 (COX-2).
- VIOXX, established trade name for rofecoxib, was approved May 20, 1999 by the Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products.
- The pharmacological class for rofecoxib is as a non-steroidal anti-inflammatory drug, specifically a selective COX-2 inhibitor.
- MRL has submitted NDA 21-042/S-026 (tablets) and NDA 21-052/S-019 (suspension) for the proposed indication for relief of signs and symptoms of JRA, subtypes polyarticular and pauciarticular, in patients ≥2 years to ≤17 years of age.
- Dose regimens included in the Phase 3 efficacy study and open-label extension are: Rofecoxib was administered as a lower-dose (0.3 mg/kg to a maximum of

12.5 mg once a day) and higher-dose rofecoxib as (0.6 mg/kg to a maximum of 25 mg once daily). Naproxen, active comparator, was administered as 15 mg/kg per day divided into two daily doses.

- Age groups studied: polyarticular and pauciarticular course JRA, patients ≥ 2 years and ≤ 17 years of age.

2.1.2 State of Armamentarium for Indication(s)

There are few approved NSAIDs and no approved selective COX-2 inhibitor with indications for relief of the signs and symptoms of polyarticular or pauciarticular course JRA. The approved NSAID alternatives to rofecoxib are Aspirin, Tolmetin Sodium (Tolectin), Ibuprofen and Naproxen. There are no placebo controlled trials in JRA using NSAIDs. Aspirin has been the most common active comparator in past JRA trials.

2.1.3 Availability of Proposed Product in the U.S.

VIOXX was initially approved May 20, 1999 for the relief of the signs and symptoms of osteoarthritis, the management of acute pain in adults and the treatment of primary dysmenorrhea. As of March 10, 2004 VIOXX is available in 41 countries, indicated for the treatment of osteoarthritis, rheumatoid arthritis, (b) (4) acute pain, dysmenorrhea in the United States (b) (4)

Major safety concerns of rofecoxib treatment as stated in the current approved label: VIOXX GI Outcomes Research (VIGOR Study) showed a higher incidence of serious cardiovascular thrombolic events (sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses) in patients treated with VIOXX 50 mg once a day as compared to patients treated with naproxen 500 mg twice per day. There is a risk of gastrointestinal ulceration, bleeding and perforation. The VIGOR Study showed a significant reduction in the risk of development of perforation, ulcer and bleeding (PUB) (e.g., symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding), including complicated PUBs in patients taking VIOXX compared to naproxen. Additional safety risks exist for anaphylactoid reactions. VIOXX is not recommended in patients with advanced renal disease and is not recommended in late pregnancy because it may cause premature closure of the ductus arteriosus. MRL is requesting labeling changes with NDA 21-042/S-026 and NDA 21-052/S-019.

2.1.4 Important Issues with Pharmacologically Related Products

There are few studies of efficacy with NSAIDS or selective COX-2 inhibitors in JRA and no placebo-controlled studies of either category of medication in JRA have been previously performed. Placebo controlled clinical trials in JRA, regardless of the subtype, are not ethically feasible due to the clinical course and morbidity of JRA when there are approved drugs with a pediatric indication for the treatment of JRA. The safety risks and adverse event profiles for naproxen, ibuprofen and tolmetin sodium are similar. Common adverse events for these NSAIDS in pediatric patients are nausea, dyspepsia, gastrointestinal distress, abdominal pain, diarrhea vomiting, constipation, gastritis and peptic ulcer; headache, elevated blood pressure, edema, dizziness, drowsiness, headache,

weight gain or weight loss, anaphylactoid reactions, urticaria, skin irritation, tinnitus, visual disturbance, small and transient decreases in hemoglobin and hematocrit, elevated BUN, hematuria, proteinuria, dysuria, urinary tract infection.

2.1.5 Pre-submission Regulatory Activity

The regulatory history for VIOXX (rofecoxib) and the two pediatric supplements, S-026 and S-019, are as follows:

- VIOXX was initially approved on May 20, 1999 for indications as described in Section 2.3.
- July 29, 1999 Merck submitted a Proposed Pediatric Written Request (PPWR) for a pediatric development program proposing two PK studies to be conducted in JRA as part of the NDA 21-042, efficacy supplement N-012, to support a RA indication. On November 29, 1999 the Division advised Merck that studies to support efficacy and safety of rofecoxib for pediatric patients with JRA would be required for pediatric exclusivity.
- In a February 8, 2000 pre-sNDA meeting, Merck and the FDA agreed that two pediatric PK studies, in addition to a large scale JRA efficacy clinical trial would be sufficient to obtain pediatric exclusivity.
- Merck revised the PPWR on August 31, 2000 outlining the initial proposed 12-week efficacy study and the 52-week open label extension study. Protocol No. 134-00 was submitted on August 23, 2000. August 31, 2000 Merck proposed that the data from the 12-week efficacy and the two PK studies be submitted to the Division by October 1, 2001 within the time period for an exclusivity determination by the Sunset date, January 2, 2002. Note: Rofecoxib is one of a class of "Sunset-Driven Products" created by Section 111 of the Food and Drug Modernization Act and Section 505A of the Food, Drug and Cosmetic Act. Sunset driven products were those products marketed after November 21, 1997 but approved prior to a Written Request (WR). VIOXX was first approved May 20, 1999. As noted by the sponsor, the existence of these exacting timelines also made it mandatory to initiate the PK studies expeditiously following the PPWR.
- As noted by the sponsor, the 120 day FDA goal date for review of the August 31, 2000 PPWR and issuance of a WR was November 30, 2000. However, the FDA notified MRL that the Division was not able to meet this goal due to competing priorities. In the absence of a WR and in face of the critical timelines discussed above, it was necessary for Merck to initiate the efficacy portion of its' pediatric development program in December 2000 in order to successfully complete the study in time to meet the statutory requirements for this Sunset-Driven Product. Timeline flexibility was discussed in two teleconferences between MRL and the Division January 17, 2001 and March 1, 2001. The RA efficacy supplement N-012, was under review at the time. Discussion included the acceptability of one efficacy supplement should the adult RA application be approved.
- On May 7, 2001 the FDA issued a WR for the study of JRA, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act. This WR extended the date of the study submission from October 1, 2001 to December 31, 2003. The Best

Pharmaceuticals for children Act (BPCA) extended the sunset Date to October 1, 2007 and, therefore, eliminated the special class of Sunset-Driven Products.

- On May 7, 2001 the WR requested the analysis of mean apparent oral clearance (CL/F) as a basis of study power and the use of the JRA Definition of Improvement ≥ 30% (JRA DOI 30) as the primary efficacy criterion.
- On December 18, 2002 a teleconference was held in which MRL agreed to revise the ongoing protocols, data analysis plans (DAP) and update the PK clinical study reports (CSR) to comply with the WR.
- On December 6, 2001 the Division issued a Revised Pediatric WR which superseded the May 7, 2001 version. The December 6, 2001 WR acknowledged the ongoing review of the adult RA rofecoxib indication and the single pediatric efficacy and safety study in response to the WR. The sponsor agreed to use age-appropriate dosage forms, such as the approved suspension, for pediatric patients between the ages of 2 years to 16 years of age and oral tablets for pediatric patients older than 11 years of age.
- On April 11, 2002 VIOXX was approved by the FDA for the relief of the signs and symptoms of rheumatoid arthritis.
- On September 13, 2002 Merck submitted an acknowledgement letter in response to the FDA's July 3, 2002 letter, re-issuing the WR under the BPCA. This submission included an overview of Merck's studies that had been or were currently being conducted to fulfill the WR. A teleconference was held on December 18, 2002 at which additional terms of the WR were clarified for PK studies in JRA patients including CL/F data as a post-hoc analysis, Merck agreed to the primary endpoint in the JRA efficacy study as the JRA DOI 30. In a follow up teleconference, FDA again recommended that the PK data from JRA patients be compared to adult RA patients. Merck agreed to and completed a PK study of rofecoxib in adults with RA.
- On May 14, 2003 FDA issued an amendment to the December 6, 2001 pediatric WR, that PK data from a pre-specified RA database be used for comparison to the JRA group, the word "studies" was changed to "study" in the description of the efficacy study and defined PK sampling take place throughout the steady state dosing interval (0 to 24 hours) as opposed to previous language about sampling throughout the "absorption and elimination phase".
- July 29, 2003, a pre-sNDA meeting was held between Merck and FDA. The Division restated to Merck (b) (4)
- There were no Advisory Committee meetings related to this submission.

2.1.6 Other Relevant Background Information

The FDA granted Merck 6 months of marketing exclusivity for VIOXX (Rofecoxib) on February 18, 2004. See Section 2.2 and 2.3 above.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

As VIOXX (Rofecoxib) is an approved drug. These two pediatric efficacy supplements did not include chemistry or microbiology reviews.

3.1.1 Chemistry (and Product Microbiology, if applicable)

Not applicable for this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1.1 Sources of Clinical Data

The data was submitted from the sponsor was in electronic format to CDER, HFD-550's Electronic Document Room (EDR) and hard copy, Volumes 1 to 6. The data quality of the submission was acceptable to this Reviewer. Additional sources of clinical data used for this review include: NDA 21-042/S-007 and subsequent submissions, NDA 21-042 (capsules) and NDA 21-052 (oral suspension), S-007 (Gastrointestinal Safety); HFD-550 Division files and related reviews: Statistics review by Atiar Rahman, PhD; Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD. Literature is referenced. No external consultations were obtained by the FDA for this review.

4.1.2 Tables of Clinical Studies

MRL submitted 6 clinical trial study reports in S-026 and S-019: four PK studies (three in JRA patients and one in adult RA patients), the Phase 3 efficacy and safety study, and the 12-month open-label extension. See **Table 1.** The sponsor's proposed indication is for the treatment of relief of the signs and symptoms of JRA in patients ≥2 years to less than or equal to 17 years of age.

Table 1. Summary of 6 Studies for Rofecoxib Pediatric Filing

Protocol #/ Study; Total # Randomized Pts.	**Entry Criteria; Age, Diagnosis**	**Objective**	**Study Design**	**Treatment**
Protocol 105; JRA, PK Study in Adolescents Total # randomized, 11	12 to 17 years w/ JRA	Study AUC of rofecoxib at steady state in adolescent JRA pts.	1) 14-day, oral dose, single-period study, rofecoxib; 2) 12-wk, double-blind efficacy period w/rofecoxib, naproxen	Part I: Daily dose of rofecoxib 12.5 or 25 mg tabs to approximate 0.322mg/kg; Part II: Daily dose rofecoxib tabs to approximate 0.322 mg/kg/day or naproxen to approximate 15 mg/kg.
Protocol 109/110 Part I: JRA PK Study in Young Children; Total # randomized 26	2 to 11 years w/ JRA	Study AUC of rofecoxib suspension in 2 - 11 yr old JRA patients, dose, wt. adjusted.	14-day, open, oral dose, single-period study of rofecoxib	Daily dose rofecoxib tabs to approximate 0.322 mg/kg
Protocol 109/110, Part II; JRA PK Study in Young Children; Total # randomized 12	2 to 5 years, pts. w/ JRA	Study AUC of rofecoxib suspension in 2 - 5 yr old JRA patients, dose wt. adjusted.	14-day open, oral dose, single-period study of rofecoxib	Daily dose to approximate 0.7 mg/kg

Protocol 134/135 Double-blind, 12 Week JRA Efficacy and Safety Study; Total # Randomized Pts. 310	2 to 17 years, pts. w/ JRA	Study the proportion of patients that improve, by JRA DOI 30 criteria, may be similar between rofecoxib & naproxen Rx.	12-wk, parallel, group, double-blind, active comparator controlled study	Patients 2 to 11 yrs. Suspension: rofecoxib 0.3 mg/kg, rofecoxib 0.6 mg/kg, or naproxen 15 mg/kg. Patients 12 to 17 yrs. Tablets: rofecoxib 12.5 mg/, rofecoxib 25 mg or naproxen 15mg/kg.
Protocol 134/135 Open Label Extension, 12 Week JRA Efficacy and Safety Study; Total # Randomized Pts. 227	2 to 17 years w/ JRA	Chronic administration of rofecoxib to JRA pts. will be safe/ well tolerated.	52-week, open-label active comparator-controlled extension.	Patients 2 to 11 years: suspension: rofecoxib 0.6 mg/kg or naproxen 15mg/kg. Patients 12 to 17 years: Tablets: rofecoxib 25 mg or naproxen 15mg/kg.
Protocol 228 Adult RA PK Study; total # Randomized Patients 12	Adults ages 21 to 65 years w/ RA	Estimate steady state PK data, after 10 days Rx in RA patients	Rofecoxib 25-mg	
JRA – Juvenile Rheumatoid Arthritis (pauci and polyarticular course); PK – Pharmacokinetic; Area Under Concentration (AUC)-time curve determination over 24 hours 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 6 variables in the core set, with no more than one of the remaining variables worsened by more than 30%. The 6 core variables are: 1) investigator global assessment of disease activity; 2) parent/patient global assessment of over-all well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) Erythrocyte Sedimentation Rate.				

4.1.3 Review Strategy

The NDA pediatric supplement review included 6 studies. Four PK studies are summarized in the Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD. Statistics review was completed by Atiar Rhaman, PhD. Safety was reviewed across all 6 studies, though the JRA patient numbers were very small in the four PK studies. The NSAID class label and the VIOXX (rofecoxib) label for adults were relied upon for adverse event comparison.

4.1.4 Data Quality and Integrity

No study sites were identified for inspection by the Division of Scientific Investigations (DSI). The Case Reports forms are acceptable and were incorporated in this Medical Officer's review of submitted materials. No special government employees (SGEs) 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/ data-entry processing and quality control were performed by MRL. This study was 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.

4.1.5 Compliance with Good Clinical Practices

No study site specific issues are noted in these studies. The informed consent documents were appropriate for parents/patients, age appropriate. The protocols, revised protocols, and informed consent form were reviewed and approved by the local Institutional Review Boards (IRB).

4.1.6 Financial Disclosures

In accordance with 21 CFR Part 54, a signed Form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) was included with these NDA Supplement submissions. 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 questions raised about integrity of data submitted.

5 CLINICAL PHARMACOLOGY

5.1.1 Pharmacokinetics (PK) See Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD.

Protocol 105

This study was an open-label, randomized study to evaluate the steady-state plasma concentration profile of rofecoxib in late-stage, post-pubertal JRA patients, 12 years to 17 years of age, (n=11). In Part I of this protocol, rofecoxib was administered as once-daily dosing for 13 days, followed by rofecoxib once daily, *or* naproxen twice-daily for 12 weeks, as Part II.

Adolescent patients who received 25 mg rofecoxib appear to show similar PK characteristics to healthy adult controls and adult RA controls who received 25 mg rofecoxib. Adolescent patients who received 12.5 mg rofecoxib had approximately half the exposure of 25mg rofecoxib in healthy adult controls. See Section 4.2, Table 1, Summary of 6 Rofecoxib Clinical Studies. See Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD.

Protocol 109

This study was an open-label, study to evaluate the steady-state plasma concentration profile of rofecoxib in JRA patients 2 years to 11 years of age receiving a rofecoxib dose of ~ 0.322mg/kg/day. Except for the outliers, exposure in this study (especially in 2 year to 5 year old patients) appears to more closely match dosing with 12.5mg in adults. For the 2 to 5 year old age group, the area under the curve (AUC) geometric mean ratio (GMR) for children compared with adult controls appears lower than for the 6 to 11 year old patients. Assuming dose proportionality, 0.6 to 0.7mg/kg rofecoxib, given across the age range of 2 to 11 years, may be more likely to approximate exposure of 25 mg in adults.

Medical Reviewer concludes that dosing by body weight appears to be important. See Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD.

Protocol 110
This study was an open-label, oral-dose study to evaluate the steady-state plasma concentration profile of rofecoxib in JRA patients 2 years to 5 years old. These children received a rofecoxib dose of ~0.7 mg/kg/day and appear to have been dosed higher, in terms of systemic exposure, relative to adult historical controls who received 25 mg. The systemic exposure of ~0.7 mg/kg/day rofecoxib in 2 to 5 year old JRA patients appears to be ~ 25% higher than that produced by 25-mg tablets in the adult reference subjects. Based on the linear PK of rofecoxib in this dose range, a dose of 0.6 mg/kg/day may be a better match for exposure of 25 mg in the adult reference patients than the dose of 0.7 mg/kg/day studied, when administered to 2 to 5 year old patients.
This Medical Reviewer recommends study of rofecoxib suspension in children less than 10 k. Weight range is more specific than age range for the most accurate dosing as JRA patients are often under weight and small for age.

Protocol 228
An open-label, single-period multiple-dose study in 12 adult Rheumatoid Arthritis (RA) patients was completed to investigate the steady-state plasma concentration profile of rofecoxib 25 mg once daily at steady state after 10 days treatment. Rofecoxib is an approved drug for the treatment of RA in adults at the dose of 25mg once daily.

5.1.2 Pharmacodynamics
See Section 5.1, PK, Protocol 105, 109 and 110, for this Medical Reviewer's comments. See Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD.

5.1.3 Exposure-Response Relationships
This Reviewer concludes the exposure was adequate in the 12-week study with the 52-week extension study based on the efficacy results. See Section 6, Integrated Review of Efficacy.

The four PK studies (three studies in JRA patients and one study in adult RA patients) were adequate to determine the dosing used in the two clinical trials. The sponsor used age as the primary metric to determine rofecoxib dose; secondarily, weight was used to determine dose only for JRA patients weighing < 40 kg. This Medical Reviewer concludes that dosing by body weight appears to be more specific because children with chronic disease, such as JRA, tend to be smaller and weigh less than their age matched peers. Therefore, weight is more specific than age for dose calculations.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: The proposed for the indication is for the relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA) for patients ≥ 2 years to ≤ 17 years old. There are no other indications sought by the sponsor from these two pediatric supplements.

6.1.1 Methods
Clinical data was received from Phase 3, efficacy and safety study, Protocol 134/135, designed as a 12-week, double-blind, active-controlled trial to evaluate the efficacy and

safety of rofecoxib for treatment of JRA. This study was conducted in JRA patients ≥ 2 years to ≤ 17 years old in 41 clinical centers in Australia, Europe, Israel, Mexico, South America and the United States.

6.1.2 General Discussion of Endpoints

The primary endpoint for evaluating efficacy in Protocol 134/135 and in the extension is the proportion of patients meeting the criteria of the Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30% (JRA DOI 30). [1] The JRA DOI 30 criterion is defined as achieving at least 30% improvement from baseline in any of 3 of 6 variables in the core set, with no more than 1 of the remaining variables worsening by greater than 30%. These 6 core components of the JRA DOI 30 are: (1) investigator's global assessment of disease activity (scored on a 100-mm VAS); (2) parent/patient's global assessment of well-being (scored on a 100-mmm 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) Erythrocyte Sedimentation Rate (ESR).

The key secondary efficacy endpoint was the proportion of patients with improvement from baseline in parent/patient's assessment of overall well-being. Other secondary efficacy endpoints included, parent/patient's global assessment of pain, proportion of patients discontinuing due to lack of efficacy, and the individual components of the JRA DOI 30 core set.

In review of changes in the protocol, the JRA DOI 30 was not initially chosen as the primary efficacy endpoint. However, the primary endpoint was changed to the JRA DOI 30 at the request of the Division. An analysis of the JRA DOI 30, a composite endpoint, was expected to provide a more adequate representation of the effects of active treatment. Hence, prior to unblinding the database, the JRA DOI 30 was chosen to replace the patient's assessment of overall well being as the primary endpoint for Protocol 134/135 and the Extension Study Protocol 134/135. Note that all of the core components of the JRA DOI 30 were prespecified in previous versions of the protocol; the change in primary endpoint mandated a change in analysis, not in the conduct of the study.

There are limitations in the JRA DOI 30 endpoint, particularly as it applies to the study of NSAIDs in JRA, as this definition was established for the study of disease modifying anti-rheumatic drugs (DMARDs). The JRA DOI 30 endpoint has never been validated in studies of NSAIDs though the 6 core variables 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 < 4 joints). In addition, the definition of improvement does not include an assessment of pain relief, yet analgesia is one of the important benefits of NSAID therapy in this disease. The proportion of patients meeting the JRA DOI 30 criteria and the proportion of patients demonstrating improvement from baseline in parent/patient's

1. Giannini EH, Ruperto N, Ravell A et al: Preliminary definition of improvement of juvenile rheumatoid arthritis, Arth Rheum 1997; 40: 1202-1209.

assessment of overall well-being was assessed by the Mantel-Haenszel estimate and resultant 95% CI for relative risk with protocol, joint involvement (pauciarticular and polyarticular course) and age group as stratification factors. The proportion of patients discontinuing test therapy due to lack of efficacy was assessed using Fisher's exact test. Continuous efficacy variables were summarized by the time-weighted average change from baseline across the 12-week treatment period, and analyzed using an Analysis of Covariance (ANCOVA) model including terms for treatment group, protocol stratum, joint involvement stratum (pauci-, polyarticular course), age group and baseline value as a 1-degree-of-freedom covariate. The primary analysis was based on a modified intention-to-treat analysis (MITT) set; a per-protocol (PP) analysis based on predefined exclusion rules was carried out for the primary endpoint to corroborate the primary analysis results. Efficacy was also examined in 2 year to 11 year old patients and in 12 to 17 year old patients.

6.1.3 Efficacy Finding and Results

EFFICACY FINDINGS
Protocol 134/135

In the Phase 3, 12-week study, Protocol 134/135, two doses of rofecoxib were tested; naproxen was selected as the active comparator. Eligible patients underwent a 72-hour washout of prior NSAID therapy and were assigned to 1 of 3 treatment groups, in approximately equal proportions: (1) lower-dose rofecoxib; 0.3 mg/kg/day in 2 to 11 year olds (not to exceed 12.5 mg/day), or 12.5 mg daily for 12 to 17 year olds; (2) higher-dose rofecoxib: 0.6 mg/kg/day in 2 to 11 year olds (not to exceed 25 mg/day), or 25 mg daily for 12 to 17 year olds; (3) naproxen, targeted to 15 mg/kg/day. Patients 2 to 11 years old received suspension formulations and 12 to 17 year olds received tablets.
See Section 10.1 for the Protocol review.

Allocations were stratified by joint involvement (e.g., pauciarticular and polyarticular disease) and age group (*sponsor's selection of age ranges to be grouped*), to obtain approximate equal numbers of 2 year to 11 year old and 12 year to 17 year old patients. The study was monitored centrally to ensure that at least 20% of patients in the younger age group were 2 year to 5 years old.

Ongoing stable DMARD therapies were permitted, but only if doses were anticipated to remain unchanged over the study course. Follow-up clinical assessments were performed at 2, 4, 8, and 12 weeks on study therapy. Acetaminophen was permitted as rescue medication for pain, but use was prohibited within 24 hours of scheduled clinic visits.
See Section 10.1, Review of Individual Study Reports, for Schedule of Study Visits.

Patient Disposition
Of the 310 patients allocated at the randomization visit (Visit 2), 285 (91.9%) completed the 12-week study. Overall, 10 (9.2%), 5 (5.0%), and 10 (9.9%) patients in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen groups, respectively, discontinued

from the base study due to adverse experiences, lack of efficacy, or other reasons. See **Table 2.**

Table 2. 12-Week Study, Protocol 134/135, Patient Accounting
(This Table is from the sponsor's submission, Table 13, Section 6.1, page 65 of 2398.)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg	Naproxen 15 mg/kg	Total
	n (%)	n (%)	n (%)	n (%)
ENTERED:	109	100	101	310
Boys	26	30	27	83
Girls	83	70	74	227[†]
COMPLETED	99 (90.8)	95 (95.0)	91 (90.1)	285 (91.9)
DISCONTINUED	10 (9.2)	5 (5.0)	10 (9.9)	25 (8.1)
Clinical adverse experiences	3 (2.8)	0 (0.0)	3 (3.0)	6 (1.9)
Laboratory adverse experiences	3 (2.8)	1 (1.0)	0 (0.0)	4 (1.3)
Lack of efficacy	3 (2.8)	4 (4.0)	4 (4.0)	11 (3.5)
Lost to follow-up	0 (0.0)	0 (0.0)	3 (3.0)	3 (1.0)
Other reasons	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)

[†] The age of AN 96 (0.6 mg/kg, higher-dose rofecoxib) was 11 years old, but was recorded as 3 years old. The date of birth was entered as 07-MAR-1998. The actual date of birth was 07-MAR-1990.

Demographics and Other Baseline Characteristics

JRA Subtypes
All ages were represented in the study population with more than 10% under 5 years old. The study population was divided between pauciarticular course JRA, 111 (46.5%), and polyarticular course JRA, 166 (53.5%). See **Table 3.**

Table 3. Baseline Joint Involvement Characteristics by Treatment Group: JRA Sub-type

	Rofecoxib			
	Lower-dose rofecoxib (N=109)	Higher-dose rofecoxib (N=100)	**Naproxen** (n=101)	**Total** (n=310)
Joint Involvement (n [%])				
Pauciarticular	49 (45.0)	49 (49.0)	46 (45.5)	144 (46.5)
Polyarticular	60 (55.0)	51 (51.0)	55 (54.5)	166 (53.5)

Patients with systemic onset JRA were excluded from the study unless they had been free of systemic symptoms for more than 3 months. The rationale for excluding systemic course JRA patients is that they often require intensive therapy with high-dose aspirin (ASA) and/or systemic corticosteroids in doses that may vary widely over the course of several weeks. Such a variation in background therapy would invalidate assessments of efficacy due to the study drug; stable doses of concomitant medications for JRA could not be required in a child with systemic JRA. Three children in the pivotal study had a history of systemic JRA or developed features of systemic JRA during the study. One patient, AN 552, was diagnosed with polyarticular JRA in 1993 which was active upon entry into the study in 2001. This patient was also reported to have had a diagnosis of

Still's disease which began in 1996 and was inactive upon entry into the study. Another child, AN116, had features consistent with systemic JRA, but this child was not labeled as systemic onset JRA by the investigator and a third child had a systemic flare during the extension study. The sponsor's decision to *not* include patients with systemic JRA course is not considered a protocol violation as the WR only "encouraged" inclusion of this subset of JRA patients. No reassessment of data is required in this study as inclusion of the three patients described is not expected to alter the outcomes.

Demographics

Of the 310 randomized patients, 227 (73.2%) were girls and 83 (26.8%) were boys. Two hundred twenty-five study subjects (72.6%) were White, 51 (16.5%) were Multi-racial, 15 (4.8%) were Hispanic American, 14 (4.5%) were Black, 1 (0.3%) was Asian, 1 (0.3%) was Eurasian, 1 (0.3%) was European, 1 (0.3%) was Indian, and 1 (0.3%) was Polynesian. See **Table 4.**

Age

The patients' ages ranged from 2 to 17 years with mean age 9.9 years, and median age 10.0 years. One hundred eighty-one (58.4%) of the patients were ≤ 11 years old, while 129 (41.6%) of the patients were > 11 years old. Forty-six (14.8%) of the patients who participated in the study were 2 to 4 years old, and 135 (43.5%) were 5 to 11 years old. Sixty-one (19.7%) of patients were 2 to 5 years old.

Table 4. 12-Week Study, Protocol 134/135, Baseline Patient Characteristics by Treatment Group (Gender, Age and Race)

(This table is from the sponsor's submission, Section 6.5, Table 15, page 73 of 2398)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)		Total (N=310)	
	n	(%)	N	(%)	n	(%)	n	(%)
Gender								
Female	83	(76.1)	70	(70.0)	74	(73.3)	227	(73.2)
Male	26	(23.9)	30	(30.0)	27	(26.7)	83	(26.8)
Age								
2 to 4 years†	15	(13.8)	22	(22.0)	9	(8.9)	46	(14.8)
5 to 11 years	50	(45.9)	38	(38.0)	47	(46.5)	135	(43.5)
12 to 17 years	44	(40.3)	40	(40.0)	45	(44.6)	129	(41.6)
Mean	9.7		9.4		10.7		9.9	
SD	4.26		4.27		3.99		4.20	
Median	10.0		10.0		11.0		10.0	
Range	2 to 17		2 to 16		2 to 17		2 to 17	
Race								
Asian	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
Black	1	(0.9)	4	(4.0)	9	(8.9)	14	(4.5)
Eurasian	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.3)
European	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
Hispanic American	6	(5.5)	4	(4.0)	5	(5.0)	15	(4.8)
Indian	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.3)
Multi-Racial	15	(13.8)	20	(20.0)	16	(15.8)	51	(16.5)
Polynesian	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
White	85	(78.0)	69	(69.0)	71	(70.3)	225	(72.6)

† The age of AN 96 (0.6 mg/kg, higher-dose rofecoxib) was 11 years old, but was recorded as 3 years old. (The date of birth was entered as 07-MAR-1998. The true date of birth was 07-MAR-1990.) Therefore, the actual number of patients in the 2- to 4-year-old range was 1 less, 45, and the actual number of patients in the 5- to 11-year-old group was 1 more, 136.

Weight
Among the 129 patients aged 12 to 17 years of age, 31 patients in the lower-dose rofecoxib treatment group were ≤ 60 kg, and 13 patients were > 60 kg. Of the 40 patients in the higher-dose rofecoxib treatment group, 34 were ≤ 60 kg, and 6 patients were > 60 kg. Of the 45 patients in the naproxen treatment group, 35 were ≤ 60 kg, and 10 patients were > 60 kg.

Secondary Diagnoses
Two hundred forty-two (78.0%) of the patients enrolled had at least one secondary diagnosis. Secondary diagnoses of infections and infestations were the most commonly reported. Secondary diagnoses of the gastrointestinal disorders were the second most commonly seen, followed by diagnoses of the respiratory, thoracic and mediastinal disorders.

Compliance
The mean compliance rates were 94.9, 96.9, and 94.2% in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively. The compliance rate was 95.3% across treatment groups. [Note: The compliance rate is the percent of the average of actual daily amount of oral suspension or dosage taken, as assessed by the amount of oral suspension or tablet counts, against the designated daily dosage.]

Concomitant Medications
Of the 310 randomized patients, 263 (84.8%) took at least one medication in addition to the study drug during the base study. Anti-neoplastic agents, analgesics, and anti-anemic preparations were the most common concomitant drug therapies. The majority of patients had been treated with NSAIDs (88.7%) of which naproxen had been used by 56.1% of patients. Consistent with the presence of polyarticular disease in 53.5% of the population, 50% of the children used DMARDs, of which methotrexate was the most common (41.6%). Tumor Necrosis Factor (TNF) sequestrants such as etanercept were used by 7.1 and 8.4% of patients during the 12-week study and during the extension, respectively. Concomitant medications were comparable across the three treatment groups.

The percentage of patients who used drugs for gastrointestinal acid related disorders was higher in the lower-dose rofecoxib 23(21.1%) and naproxen treatment groups 23(22.8%), as compared to 11(11.0%) of patients in the higher-dose rofecoxib treatment group. The percentage of patients who used systemic anti-infective therapy was higher in the lower-dose rofecoxib and higher-dose rofecoxib treatment groups. Twenty-one (19.3%), 26 (26.0%) and 9(8.9%) of the patients in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively, used systemic anti-infective therapy.

Prior Medications
The majority of patients had previously been treated with NSAIDs (88.7%); naproxen was the most common prior NSAID (56.1%). Half of the patients were treated with DMARDS; the most common DMARD was methotrexate (41.6%). According to the sponsor, 252 (81.3%) of patients had taken an NSAID or a selective COX-2 inhibitor on the day of the first study visit. Both celecoxib and rofecoxib had been used to treat some

patients prior to the study. Other common prior medications included anti-anemia preparations taken by 29 (26.6%), 28 (28.0%), and 26 (25.7%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen treatment groups, respectively. Most commonly given was folic acid, which is often used concomitantly with methotrexate.

Protocol Violations / Deviations
Patients who deviated from the protocol were excluded, as appropriate, from analyses of efficacy and safety. All patients who violated the protocol in predefined, significant ways were excluded from the PP analysis. None of the treatment assignments was prematurely unblinded. See Section 10.1

Endpoints and their Statistical Analyses
The primary analysis for the primary endpoint was the proportion of patients achieving the JRA DOI 30 criteria regardless of the completion status. The proportion of patients meeting the JRA DOI 30 criteria and completing the 12-week-treatment period was examined as a secondary analysis of this endpoint. The proportion of patients meeting the JRA DOI 30 criteria and the proportion of patients demonstrating improvement from baseline in parent/patient's assessment of overall well-being were assessed by the Mantel-Haenszel estimate and resultant 95% CI for relative risk with protocol, joint involvement and age group as stratification factors. The analysis of covariance (ANCOVA) model, which included terms of treatment and stratification factors (protocol, joint involvement, and age group) as main effects and baseline value as a 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 the treatment response was done through graphical presentation of the LS mean changes from baseline, with standard error (SE) shown on plots.

Dispositions
Discontinuations Due to Lack of Efficacy
The proportion of patients discontinuing study therapy due to lack of efficacy was assessed using Fisher's exact test. Life-table plots of the proportions of patients remaining in the study after removing those discontinued during the base study due to lack of efficacy, adverse experiences, or other reasons were also provided. A per-protocol analysis, based on predefined exclusion rules, was carried out for the primary endpoint to corroborate the primary analysis results. The discontinuation rates due to lack of efficacy were (b) (4) 4/100 (4.0%) and 4/101 (4.0%), for the (b) (4) higher-dose rofecoxib, and naproxen treatment groups, respectively. See **Table 5**. None of the comparisons by secondary efficacy endpoints achieved statistical significance.

Table 5. 12-Week Study, Protocol 134/135, Analysis of Endpoint: Discontinuation Due to Lack of Efficacy
(This table is from the sponsor's submission, Table 25, Section 7.2.3, page 100 of 2398.)

Treatment		Frequency (%)	
Lower-Dose Rofecoxib		3/109 (2.8%)	
Higher-Dose Rofecoxib		4/100 (4.0%)	
Naproxen		4/101 (4.0%)	
Between-Group Comparisons	Differences in Percent	(95% C.I.)	p-value †
Higher-Dose Rofecoxib vs. Naproxen	0.04	(-5.37, 5.44)	>0.999
Lower-Dose Rofecoxib vs. Naproxen	-1.21	(-6.10, 3.68)	0.713
Higher-Dose vs. Lower-Dose Rofecoxib	1.25	(-3.67, 6.17)	0.712
† From Fisher's exact test.			

The treatment effect among patients who completed the 12-week study was evaluated for the primary endpoint as requested by the Division. Since 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 and that of the JRA DOI 30 *responder and completer* yielded the same results. (b) (4)

[redacted]

Statistical Analyses Not Performed
The analyses of the JRA DOI 30 core set of variables stratified by drop-out pattern and by time of drop-out were not carried out because there were too few patients who discontinued due to various reasons (less than 6 patients per treatment group) to yield meaningful statistical results.

EFFICACY RESULTS

Primary Endpoint

(b) (4)

[redacted] This review was conducted using a non-inferiority point estimate lower limit margin of ≥ 0.75, (b) (4) the higher-dose of rofecoxib achieved non-inferiority to naproxen, lower limit was 0.98 95%CI (**0.76**, 1.26), in a modified intent-to-treat analysis, JRA DOI 30 responder, *regardless of completion status*. Similarly, the higher-dose of rofecoxib achieved non-inferiority to naproxen, lower limit was 1.00 95%CI (**0.78**, 1.29), in a modified intent-to-treat analysis, by the JRA DOI 30 *responder and completer status*. *(Lower limit is in **bold font.**)

(b) (4)

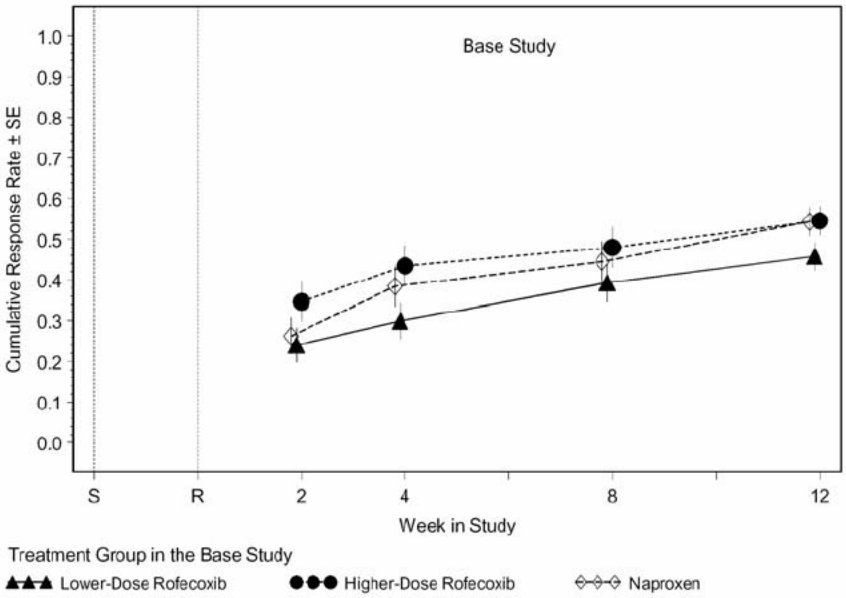
See **Table 6, Figure 1.**

Using the MITT population, the higher-dose rofecoxib and naproxen treatment groups achieved the JRA DOI 30 response of 54.5% and 55.1%, respectively. Using the Intent-To Treat, Last Observation Carried Forward (ITT-LOCF) population, the higher-dose rofecoxib and naproxen treatment groups achieved the JRA DOI 30 response of 54.5% and 53.5%, respectively. The per protocol analysis with higher dose rofecoxib versus naproxen, using the responder rate ratio from the JRA DOI 30, regardless of completion status, was estimated to be 1.04 (**0.80**, 1.35) by the sponsor. The per protocol analysis for higher dose rofecoxib versus naproxen, responder and completer analysis, demonstrated 1.08 (**0.83**, 1.42) at the 95% CI. (b) (4)

Table 6. 12-Week Study, Protocol 134/135, Analysis of Primary Endpoint: Proportion of Patients Achieving the JRA DOI 30 by Modified-Intent-To-Treat Methodology (MITT)
(This Table is from the sponsor's submission, Table 21, Section 7.1, page 91 of 2398)

JRA 30 Responder: Regardless of Completion Status (Primary)[†]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	54 /99 (54.5)	
Naproxen	54 /98 (55.1)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher Dose Rofecoxib vs. Naproxen	0.98 (0.76, 1.26)	-1.3 (-15.1, 12.5)
(b) (4)		
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	54 /99 (54.5)	
Naproxen	53 /99 (53.5)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher Dose Rofecoxib vs. Naproxen	1.00 (0.78, 1.29)	0.1 (-13.7, 13.8)
(b) (4)		

Figure 1. 12-Week Study, Protocol 134/135, Proportion of Patients Meeting the JRA DOI 30, Regardless of Completion Status Over time (Modified Intention to Treat Approach) (This figure is from the sponsor's submission, Figure 4, Section 7.1, page 92 of 2398)



SE – Standard Error; S – Screening; R – Randomization (Baseline); Screening to Baseline = Washout period for prior JRA therapy

According to the sponsor, similar to results in the 2 year to 17 year old population, for 12 year to 17 year old patients, the proportion of patients meeting the JRA DOI 30 criteria in the higher-dose rofecoxib group was not inferior to that in the naproxen treatment group.

(b) (4)

See **Table 7.**

Table 7. Analysis of the Primary Endpoint: Proportion of Patients Achieving the JRA DOI 30 Criteria During the 12-Week Study in 12 to 17 year old Patients (MITT analysis)
(This Table is from the sponsor's submission, Table 34, Section 7.3, page 119 of 2398)

JRA 30 Responder: Regardless of Completion Status (Primary)[†]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	21 /40 (52.5)	
Naproxen	26 /45 (57.8)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	0.88 (0.60, 1.29)	-7.1 (-28.1, 13.9)
(b) (4)		
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	21 /40 (52.5)	
Naproxen	25 /45 (55.6)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	0.91 (0.62, 1.34)	-5.2 (-26.1, 15.8)
(b) (4)		

† The numerator is number of patients who met the JRA 30 criteria; the denominator is the number of patients with evaluable JRA 30 criteria.
‡ From Mantel-Haenszel estimate with protocol and joint involvement as stratification factors.
§ From the normal approximation for a Cochran-Mantel-Haenszel (CMH) weighted average of the differences over all strata.
‖ In order to be a responder, the patient had to complete the 12-week study and meet the JRA 30 criteria; but to be a non-responder; the patient either did not complete the 12-week study or did not meet the JRA 30 criteria.
JRA = Juvenile Rheumatoid Arthritis.

(b) (4)

(b) (4)

(b) (4)

Secondary Endpoints

The proportion of JRA patients demonstrating improvement from baseline in the parent/patient assessment of overall well-being was (b) (4) 76.0% and 73.0%, (b) (4) higher-dose rofecoxib and naproxen, respectively. (b) (4)

See **Table 8.**

Table 8. 12-Week Study, Protocol 134/135, Analysis of Key Secondary Endpoint: Proportion of Patients Demonstrating Improvement from Baseline, Parent/Patient's Assessment of Overall Well-Being (MITT approach)

(This table is from the sponsor's submission, Table 23, Section 7.1, page 79 or 2398.)

Treatment	Frequency[†] (%)	
(b) (4)		
Higher-Dose Rofecoxib	76 /100 (76.0)	
Naproxen	73 /100 (73.0)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	1.04 (0.89, 1.22)	3.1 (-8.8, 15.0)
(b) (4)		

† Frequency = m/n, where n is the total number of patients with nonmissing values, and m is the number of patients with improvement from baseline in patient/parent's assessment of overall well-being.
‡ From Mantel-Haenszel estimate with protocol, age group, and joint involvement as stratification factors.
§ From the normal approximation for a Cochran-Mantel-Haenszel (CMH) weighted average of the differences over all strata.

(b) (4)

The mean change from baseline for (b) (4) higher-dose rofecoxib and naproxen was (b) (4) -13.61 and -9.11, respectively. Note: the larger the negative value, the better the clinical improvement. See **Table 9.**

Table 9. 12-Week Study, Analysis of Endpoint: Parent/Patient's Global Assessment of Pain Mean Change from Baseline (Flare/Randomization Visit) Time Weighted Average (Modified Intention-to-Treat Approach)

(This Table is from the sponsor's submission, Table 24, Section 7.2.2, page 98 of 2398.)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
(b) (4)							
Higher-Dose Rofecoxib	100	41.85	28.24	-13.61	24.51	-13.12	(-16.75, -9.48)
Naproxen	100	42.71	33.60	-9.11	22.49	-8.43	(-11.98, -4.88)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
Between Active Treatments			
Higher-Dose Rofecoxib vs. Naproxen	-4.69	(-9.68, 0.30)	0.065
(b) (4)			

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	17.83
Protocol	0.140	
Age Group	0.647	
Joint Involvement	0.937	
Treatment	0.132	

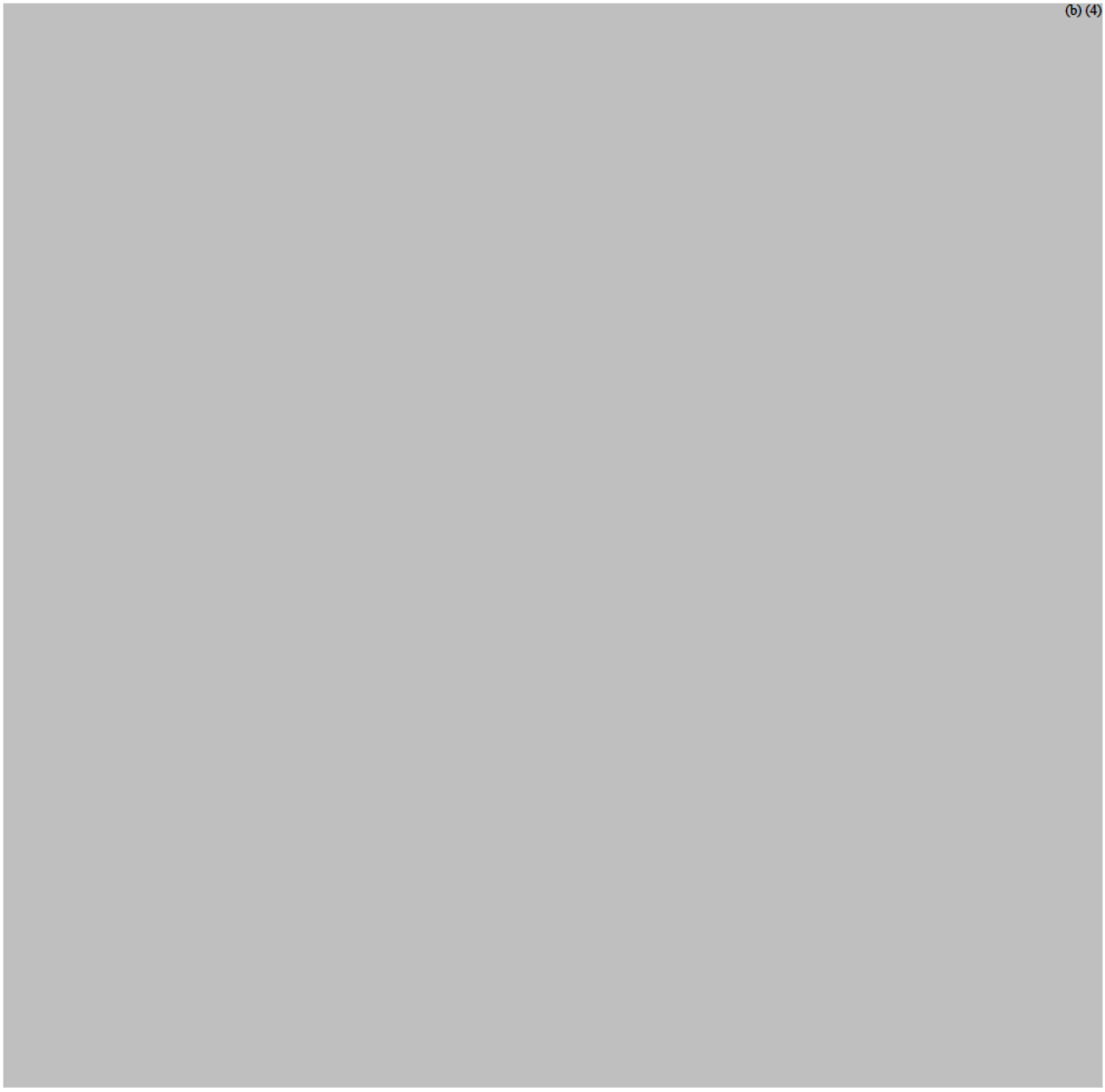
† Least-squares mean.

(b) (4)

Table 10. 12-Week Study, Analysis of Primary and Secondary Key Endpoints: Higher-Dose Rofecoxib versus Naproxen (Table is from the sponsor's submission, Table 2.5:2)

JRA 30 Core Set of Variables	Higher-Dose Rofecoxib Versus Naproxen
Primary Endpoint: Ratio of Response Rates (95% CI)[†]	
Proportion of Patients Meeting JRA30 Response Criteria (Regardless of Completion Status) Proportion of Patients Meeting JRA30 Response Criteria (Responder and Completer)	0.98 (0.76, 1.26) 1.00 (0.78, 1.29)
Key Secondary Endpoint (95% CI)[†]	
Proportion of Patients With Improvement From Baseline in Parent/Patient's Assessment of Overall Well-Being	1.04 (0.89, 1.22)
Secondary Endpoint Not Included in JRA30 Core Set: LS Mean Difference in Change From Baseline (95% CI)[‡]	
Parent/Patient's Global Assessment of Pain	-4.69 (-9.68, 0.30)
JRA Core Set: LS Mean Difference in Change From Baseline (95% CI)[‡]	
Parent/Patient's Assessment of Overall Well-Being Investigator Global Assessment of Disease Activity Functional Ability Number of Joints With Active Arthritis Number of Joints With Limited Range of Motion	-3.52 (-8.14, 1.10) -1.21 (-4.80, 2.37) -0.03 (-0.12, 0.07) 0.37 (-0.48, 1.22) 1.02 (0.14, 1.89)
LS Mean Ratio (95% CI)[§]	
Erythrocyte Sedimentation Rate (ESR)	0.91 (0.77, 1.08)

[†] This comparison is a ratio of response rates. A value >1.0 indicates that the first treatment in the comparison was favored.
[‡] This comparison is a difference in the change from baseline. A negative value indicates that the first treatment in the comparison was favored.
[§] This comparison is a ratio of values. A value <1.0 indicates that the first treatment in the comparison was favored.
LS = Least Square; CI = Confidence Interval.



(b) (4)

(b) (4)

(b) (4)

Additional Analyses

Primary and Secondary Endpoint Comparison by *Age Group*

(b) (4)

See **Tables 13** and **14.**

Table 13. 12-Week Study, Analysis of the Primary Endpoint: Proportion of Patients Meeting the JRA DOI 30: 2 to 11 Year Old Patients (MITT approach)
(This table is from the sponsor's submission, Table 33, Section 7.3, page 117 of 2398)

JRA 30 Responder: Regardless of Completion Status (Primary)[†]		
Treatment	Frequency (%)	
		(b) (4)
Higher-Dose Rofecoxib	33 /59 (55.9)	
Naproxen	28 /53 (52.8)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher Dose Rofecoxib vs. Naproxen	1.06 (0.75, 1.49)	3.0 (-15.3, 21.3)
		(b) (4)
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
		(b) (4)
Higher-Dose Rofecoxib	33 /59 (55.9)	
Naproxen	28 /54 (51.9)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher Dose Rofecoxib vs. Naproxen	1.08 (0.76, 1.52)	4.0 (-14.3, 22.2)
		(b) (4)

Table 14. 12-Week Study, Analysis of Primary Endpoint: Proportion of Patients Meeting the JRA DOI 30: Patients 12 to 17 Years Old
(This Table is from the sponsor's submission, Table 34, Section 7.3, page 119 of 2398)

JRA 30 Responder: Regardless of Completion Status (Primary)[†]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	21 /40 (52.5)	
Naproxen	26 /45 (57.8)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	0.88 (0.60, 1.29)	-7.1 (-28.1, 13.9)
(b) (4)		
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
(b) (4)		
Higher-Dose Rofecoxib	21 /40 (52.5)	
Naproxen	25 /45 (55.6)	
Between-Group Comparison	Relative Risk[‡] (95% CI)	Difference[§] (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	0.91 (0.62, 1.34)	-5.2 (-26.1, 15.8)
(b) (4)		

Parent/Patient Assessment of Overall Well-Being and Parent/Patient Global Assessment of Pain by *Age*

(b) (4)

See **Table 15.**

Table 15. 12-Week Study, Analysis of Key Secondary Endpoint: Proportion of Patients Demonstrating Improvement from Baseline in Parent/Patient Assessment of Overall Well-Being in 2 Year to 11 Year Old Patients.
(This Table is from the sponsor's Table 35, Section 7.3, page 121 of 2398)

Treatment	Frequency† (%)	
		(b) (4)
Higher-Dose Rofecoxib	45 /60 (75.0)	
Naproxen	39 /55 (70.9)	
Between-Group Comparison	Relative Risk‡ (95% CI)	Difference§ (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	1.05 (0.84, 1.32)	3.8 (-12.4, 20.0)
		(b) (4)

† Frequency = m/n, where n is the total number of patients with nonmissing values, m is the number of patients with improvement from baseline in patient/parent assessment of overall well being.
‡ From Mantel-Haenszel estimate with protocol, age group, and joint involvement as stratification factors.
§ From the normal approximation for a Cochran-Mantel-Haenszel weighted average of the differences over all strata.

Table 16. 12-Week Study, Analysis of the Key Secondary Endpoint: Proportion of Patients Demonstrating Improvement from Baseline in Parent/Patient's Assessment of Overall Well-Being in 12 to 17 Year Old Patients.
(This Table is from the sponsor's Table 36, Section 7.3, page 123 of 2398)

Treatment	Frequency† (%)	
		(b) (4)
Higher-Dose Rofecoxib	31 /40 (77.5)	
Naproxen	34 /45 (75.6)	
Between-Group Comparison	Relative Risk‡ (95% CI)	Difference§ (95% CI)
Higher-Dose Rofecoxib vs. Naproxen	1.03 (0.82, 1.29)	2.2 (-15.1, 19.5)
		(b) (4)

† Frequency = m/n, where n is the total number of patients with nonmissing values, m is the number of patients with improvement from baseline in patient/parent assessment of overall well being.
‡ From Mantel-Haenszel estimate with protocol, age group, and joint involvement as stratification factors.
§ From the normal approximation for a Cochran-Mantel-Haenszel weighted average of the differences over all strata.

Parent/Patient's Global Assessment of Pain by *Age*

(b) (4)

See **Table 17** and **18**.

Table 17. 12-Week Study, Analysis of Parent/Patient's Global Assessment of Pain Mean change from Baseline (Flare/Randomization Visit) Time-weighted Average in 2 to 11 Year Old Patients

(This Table is from the sponsor's submission, Table 38, Section 7.3, page 127 of 2398)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean Change	95% CI for LS Mean† Change
							(b) (4)
Higher-Dose Rofecoxib	60	41.80	27.26	-14.54	24.84	-13.58	(-18.09, -9.07)
Naproxen	55	42.60	35.94	-6.66	22.53	-5.46	(-10.10, -0.82)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
Between Active Treatments			
Higher-Dose Rofecoxib vs. Naproxen	-8.12	(-14.52, -1.71)	0.013
			(b) (4)

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	17.34
Protocol	0.456	
Joint Involvement	0.315	
Treatment	0.014	

Least-squares mean.

Table 18. Analysis of Parent/Patient's Global Assessment of Pain Mean change from Baseline (Flare/Randomization Visit) Time-weighted Average Over the 12-Week Study in 12 to 17 Year Old (Table is from the sponsor's submission, Table 38, Section 7.3, page 127 of 2398)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean Change	95% CI for LS Mean† Change
							(b) (4)
Higher-Dose Rofecoxib	40	41.93	29.71	-12.22	24.24	-11.79	(-17.83, -5.75)
Naproxen	45	42.84	30.75	-12.10	22.33	-11.48	(-17.05, -5.91)

Comparisons Between Treatment Groups	Difference In LS Mean	95% CI for Diff.	p-Value
Between Active Treatments			
Higher-Dose Rofecoxib vs. Naproxen	-0.31	(-8.24, 7.61)	0.938
			(b) (4)

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	18.32
Protocol	0.145	
Joint Involvement	0.231	
Treatment	0.852	

Least-squares mean.

Secondary Efficacy Endpoint Subgroups

(b) (4)

[redacted]

Medical Reviewer Comments, Protocol 134 /135

Children with chronic disease are often smaller in height and weight than their healthy peers and, therefore, do not conform to normal growth observed in healthy children and adolescents. Therefore, the clinical data were analyzed by smaller pooled age groups, ≥ 2 to < 5years, ≥6 to < 11 years and ≥12 to ≤17 years, to better understand efficacy in patients with JRA. See ***Table 19*** *and* ***20.***

Table 19. Age and Weight Categories Used for Analysis

Sponsor Analysis	Medical/Statistical Review Analysis
By Age (Years)	
≥ 2 to ≤ 11	≥ 2 to < 5
	≥ 6 to < 11
≥ 12 to ≤ 17	≥ 12 to ≤ 17
By Weight (Kilograms)	
	≥ 10 to < 20
	≥ 20 to < 40
≤ 60	≥ 40 to < 60
≥ 60	≥ 60

Table 20. 95% Confidence Intervals for JRA DOI 30 Responder Rates during the 12-Week Study by Bodyweight (Base Study: Regardless of Completion) ***Post Hoc Analysis***

6.1.4 Assuming missing value as missing

Dose Groups	Bodyweight Sub-Group (Kg)	Age (Years) n, Mean (Min, Max)	Number of Patients	Relative Risk (95% CI)
Higher Dose Rofecoxib vs. Naproxen	All Bodyweight Group	197, 10.15 (2.00, 17.00)	54/99, 54/98	0.99 (0.76, 1.28)
Higher Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	41, 4.05 (2.00, 7.00)	15/25, 9/16	1.07 (0.62, 2.10)
Higher Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	75, 9.77 (6.00, 15.00)	20/38, 19/37	1.03 (0.64, 1.63)
Higher Dose Rofecoxib vs. Naproxen	Bodyweight>=40	81, 13.58 (3.00, 17.00)	19/36, 26/45	0.91 (0.59, 1.36)

(b) (4)

6.1.5 Assuming missing value as failure

Higher Dose Rofecoxib vs. Naproxen	All Bodyweight Group	201, 10.07 (2.00, 17.00)	54/100, 54/101	1.01 (0.78, 1.31)
Higher Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	43, 4.00 (2.00, 7.00)	15/26, 9/17	1.09 (0.62, 2.16)
Higher Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	76, 9.76 (6.00, 15.00)	20/38, 19/38	1.05 (0.65, 1.67)
Higher Dose Rofecoxib vs. Naproxen	Bodyweight >=40	82, 13.55 (3.00, 17.00)	19/36, 26/46	0.93 (0.60, 1.40)

(b) (4)

(b) (4) *The parent/patient overall assessment of pain was measured and both doses of rofecoxib were numerically superior to naproxen for relief of pain, though neither rofecoxib dose was statistically significant different than naproxen. Naproxen demonstrated, numerically better and statistically significant, improvement in the number of joints with limited range of motion compared to both doses of rofecoxib. Rofecoxib demonstrated numerically better improvement in the assessment of overall well-being but was not statistically significant.*

Discontinuation rates due to lack of efficacy were not statistically significantly different, (b) (4) *4.0 and 4.0%,* (b) (4) *higher-dose rofecoxib and naproxen, respectively.*

(b) (4)

Medical Reviewer Comments, Efficacy Results, Protocol 105, 109 and 110
The three PK trials in JRA patients were not efficacy studies (Note: Protocol 228 was in adults with RA) rather exploratory studies due to the small number of studied patients, no placebo group or active comparator. The sponsor did, however, investigate JRA improvement with the following efficacy measurements: patient's assessment of overall well being visual analog scale (VAS); investigator's global assessment of disease activity (VAS); functional ability (CHAQ); number of joints with active arthritis; number of joints with limited range of motion; and C-reactive protein. Only Protocol 105 was long enough in duration, 14 weeks, to report efficacy implications. There was a suggestion of improvement, based on the mean change from baseline, for the global assessment of overall well-being, the global assessment of disease activity over time (100-mm VAS) and the joint count assessment, each by week 14. No efficacy conclusions may be may be made from these limited observations.

52-Week Open-Label Extension, Protocol 134/135

The 52-week extension study following the 12-week study, Protocol 134/135, was designed to investigate chronic administration of rofecoxib for tolerability and durability in JRA patients 2 years to 17 years old.

Baseline Demographic Characteristics

Of the 227 randomized patients in the extension study, 166 (73.1%) were girls and 61 (26.9%) were boys and the sample study was predominately White, 162 (71.4%). Patient ages ranged from 2 years to 17 years, mean age of 10.0 years, and median age 11.0 years. One hundred twenty-five (55.1%) of the pediatric patients were ≤ 11 years old; 102 (44.9%) were > 11 years old. Thirty-six (15.9%) of the study patients were 2 to 4 years old and 89 (39.2%) were 5 to 11 years old. Baseline demographic characteristics were similar between patients who elected to enter the extension and patients who entered the 12-week study but did not enter the extension. See **Table 21**.

Table 21. Baseline Patient Characteristics by Treatment Group for Patients Who Entered the 52-Week Open-Label Extension: Gender, Age, Race and Weight
(This Table is from the sponsor's submission, Table 14, Section 6.5, page 64 of 2044.)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)		Total (N=227)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	117	(73.1)	49	(73.1)	166	(73.1)
Male	43	(26.9)	18	(26.9)	61	(26.9)
Age (Years)						
2 to 4 years†	23	(14.4)	12	(17.9)	36	(15.9)
5 to 11 years	67	(41.9)	23	(34.3)	89	(39.2)
12 to 17 years	70	(43.8)	32	(47.8)	102	(44.9)
Mean	10.0		10.1		10.0	
SD	4.13		4.45		4.24	
Median	11.0		11.0		11.0	
Range	2 to 17		2 to 17		2 to 17	
Race						
Asian	1	(0.6)	0	(0.0)	1	(0.4)
Black	6	(3.8)	1	(1.5)	7	(3.1)
Eurasian	0	(0.0)	1	(1.5)	1	(0.4)
European	0	(0.0)	1	(1.5)	1	(0.4)
Hispanic American	8	(5.0)	3	(4.5)	11	(4.8)
Multi-Racial	28	(17.5)	15	(22.4)	43	(18.9)
Polynesian	1	(0.6)	0	(0.0)	1	(0.4)
White	116	(72.5)	46	(68.7)	162	(71.4)
Weight of Patients 12 to 17 Years Old						
≤60 kg	59	(36.8%)	26	(38.8%)	85	(37.4%)
>60 kg	11	(6.9%)	6	(9.0%)	17	(7.5%)

† One patient, AN 96 (high-dose rofecoxib), who was 11 years old was incorrectly recorded in the database as 3 years old.

Treatment Group Assignment
Patients who continued in the 52-week extension were a self-selected, non-randomized subset. JRA patients who elected to enter the extension generally showed greater clinical improvements (e.g., response to treatment consistent with therapeutic benefit) compared with JRA patients who entered the 12-week study but did not enter the 52-week extension. In the 52-week extension, only higher-dose rofecoxib was administered; naproxen remained the active comparator.

JRA patients **2 to 11 years** of age received rofecoxib or naproxen as a suspension formulation dosed by weight. See **Table 22.** Patients assigned to naproxen group received a 0.3-mL/kg twice-daily dose of 25 mg/mL naproxen suspension. JRA patients **12 to 17 years** of age received rofecoxib 25 mg tablets once daily regardless of weight. Patients assigned to naproxen received 375 mg or 500 mg twice daily to approximate

15-mg/kg daily dose. To achieve this, patients were stratified by weight, ≤60 kg or >60 kg, with treatment shown in **Table 23.**

Table 22. 52-Week Extension Treatment Assignments: 2 year to 11 year old patients
(This Table is from the sponsor's Table 2, Section 5.4, page 32 of 2044)

Group	Rofecoxib Treatment	Naproxen Treatment
High-dose rofecoxib Naproxen	5.0-mg/mL rofecoxib suspension None	None 25-mg/mL naproxen suspension

Table 23. 52-Week Extension Assignments: 12 year to 17 year old patients
(This Table is from the sponsor's Table 3, Section 5.4, page 32 of 2044)

Group	Rofecoxib Treatment	Naproxen Treatment
Rofecoxib 25 mg Naproxen	Rofecoxib 25-mg tablets None	None Naproxen 375-mg or 500-mg tablets†
† Patients received naproxen 375 mg or 500 mg twice daily, to best approximate 15-mg/kg total daily dose.		

The number of patients in the two treatment groups was unbalanced, with 160 patients in the rofecoxib treatment group and 67 patients in the naproxen treatment group. See **Table 24.**

Table 24. 52-Week Extension, Protocol 134/135, Treatment Assignment in the 12-Week (Base) Study and 52-Week Open-Label Extension
(This table is from the sponsor's submission, Table 22, Section 7.0, page 82 of 2044)

Base/Extension Treatment Groups	Extension Treatment Groups
Lower-Dose Rofecoxib/Higher-Dose Rofecoxib (N=58) Higher-Dose Rofecoxib/Higher-Dose Rofecoxib (N=60) Naproxen/Higher-Dose Rofecoxib (N=42)	Higher†-Dose Rofecoxib (N=160)
Lower-Dose Rofecoxib/Naproxen (N=15) Higher-Dose Rofecoxib/Naproxen (N=17) Naproxen/Naproxen (N=35)	Naproxen (N=67)
† Patients received only maximum higher-dose (rofecoxib 0.6 mg/kg, maximum 25 mg) in the extension. Therefore, this treatment group is referred to as "rofecoxib" throughout. N=Number of patients who entered the extension study in each treatment group.	

Patient Disposition

It is important to emphasize that patients who elected to enter the extension generally showed greater clinical improvements (i.e., response to treatment consistent with therapeutic benefit) compared with patients who entered the base study but did not enter the extension. See **Table 25**.

Table 25. 52-Week Extension, Patient Accounting
(This Table is taken from the sponsor's submission, Table 12, Section 6.1, page 57 of 2044.)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg	Naproxen 15 mg/kg	Total
	n (%)	n (%)	n (%)
COMPLETED BASE STUDY			285
ENTERED:	160	67	227
COMPLETED:	134 (83.8)	47 (70.1)	181 (79.7)
DISCONTINUED:	26 (16.3)	20 (29.9)	46 (20.3)
Clinical adverse experience	4 (2.5)	8 (11.9)	12 (5.3)
Laboratory adverse experience	2 (1.3)	0 (0.0)	2 (0.9)
Lack of efficacy	3 (1.9)	1 (1.5)	4 (1.8)
Other reasons	17 (10.6)	11 (16.4)	28 (12.3)

Statistical Analyses
Analyses were based on the MITT approach. There was no per protocol analysis for the open-label extension study.

CONCLUSIONS, 52-Week Extension

The 52-week open-label extension results, with the JRA DOI 30 response rates for maintenance of improvement from baseline, were 57.9% and 42.2%, rofecoxib and naproxen, respectively. (b) (4) Similarly, the 52-week extension results appear to support durability for maintenance of improvement over baseline of rofecoxib as compared to naproxen.

6.1.6 Clinical Microbiology

Clinical microbiology review is not applicable in this pediatric supplement submission. Naproxen, active comparator, is an approved drug for patients with JRA. Rofecoxib is an approved drug in adult patients.

6.1.7 Efficacy Conclusions

This Medical Reviewer concludes that (b) (4) 0.6mg/kg per day to a maximum of 25 mg per day, achieved non-inferiority by the point estimate lower limit of ≥ 0.75 (95% CI) for the JRA DOI 30 responder rate ratio. (b) (4)

(b) (4) The parent/patient overall assessment of pain, though this measure is not a core variable of the JRA DOI 30, demonstrated improvement with rofecoxib and naproxen. This Reviewer concludes that both doses of

rofecoxib were numerically superior to naproxen for relief of pain, though neither rofecoxib dose was statistically significant to naproxen. Naproxen showed numerically better improvement in the number of joints with limited range of motion and rofecoxib demonstrated numerically better improvement in overall well-being.

The 52-week open-label extension results with the JRA DOI 30 response rates for maintenance of improvement from baseline were consistent with the 12-week, double-blind study. The proportion of JRA DOI 30 responder rates appear to be supportive of durability within the 52-week extension for maintenance of improvement over baseline for rofecoxib compared to naproxen.

This Reviewer concludes that higher dose rofecoxib offers this conclusion with acceptable safety results in patients with pauciarticular and polyarticular JRA based on the primary efficacy endpoint JRA DOI 30, the 6 core variables and secondary efficacy endpoints. The small number of JRA patients enrolled in these two clinical trials was limited, even though the 12-week efficacy study represents the largest JRA study (310 pediatric patients) to date with NSAID/COX-1/COX-2 therapy. Additional Phase IV PK data is recommended to better understand dosing in JRA patients ≥ 42 kg and to better understand efficacy in adolescent JRA patients ≥ 42 kg.

7 INTEGRATED REVIEW OF SAFETY

Safety and tolerability were assessed by review of all safety parameters, physical examinations, vital signs, weight, laboratory safety and reporting of adverse events. The safety population was defined as the MITT population. The MITT analysis was the primary and only analysis for safety endpoints. No exclusions were made from the safety analyses, nor were safety data impute. Measurements of laboratory variables at post study visit were not included, but adverse experiences, which occurred within 14 days of the last test therapy were included.

7.1.1 Methods and Findings

SAFETY REVIEW

12-Week Study and 52-Week Open-Label Extension

Patient Exposure

Three hundred ten patients were randomized into the 12-week study. Two hundred eighty-five (91.9%) of 310 patients completed the 12-week study. Of these 285 patients, 227 (79.6%) entered the open-label extension. See **Table 2** (*12-week study*) and **Table 25** (*52-week extension*). In the **12-week study** and the **52-week extension**, JRA patients ages 2 years to 11 years old received suspension formulations of study medication dosed by **weight**, while 12 year to 17 year old patients received tablets, dosed by **age**. Therefore, the extent of exposure was assessed separately for 2 year to 11 year old patients and 12 year to 17 year old patients. For patients 2 years to 11 years old, the extent of exposure in all 3 treatment groups in mg/kg was calculated using the baseline

weight. Patients allocated to the lower dose rofecoxib treatment group received 0.3 mg/kg of study medication. Patients allocated to the higher-dose rofecoxib treatment group received 0.6 mg/kg of study medication.

In the **12-week study**, in **2 year to 11 year old patients**, group, the majority of patients received the protocol-specified dose of study medication: 64 of 65 patients in the lower-dose rofecoxib treatment group received a dose of >0.2 and ≤ 0.4 mg/kg, 60 of 60 patients in the higher-dose rofecoxib treatment group received >0.45 and ≤ 0.75 mg/kg, and 55 of 56 patients in the naproxen treatment group received >10 and ≤ 20 mg/kg. Pediatric patient exposure was adequate in the 12-week study.

In the **12-week study**, in the **12 to 17 year old age group**, all patients in the rofecoxib treatment group received the protocol specified dose of study medication. There were 45 patients aged 12 to 17 years old in the naproxen treatment group: 35 were ≤ 60 kg and received a total daily dose of 750 mg naproxen, the dose prescribed for patients ≤ 60 kg; and 10 patients >60 kg and received a total daily dose of 1000 mg, the dose prescribed for patients >60 kg.

In the **52-week open-label extension**, in the **2 year to 11 year old age group**, the majority of patients received the protocol-specified dose of study medication: 87 of 90 patients in the rofecoxib treatment group received a dose >0.45 mg/kg and 0.75 mg/kg and 35 of 35 patients in the naproxen treatment group received a dose >10 and ≤20 mg/kg. Three patients (AN 48, AN 100, and AN 105) 2 years to 11 year old, in the rofecoxib treatment group, received doses of 0.45 mg/kg. The mean dose for these 3 patients was 0.41 mg/kg (range 0.39 to 0.43 mg/kg). Four patients in the rofecoxib treatment group received doses of study drug >0.75 mg/kg. The mean dose for these 4 patients was 0.9 mg/kg (range 0.76 to 1.1 mg/kg).

In the **52-week open-label extension**, in the **12 to 17 year old age group**, all 70 of the patients in the rofecoxib treatment group received the protocol specified dose of study medication. A single patient (AN 504) took 2 doses of study medication on a single day. Of the 32 patients aged 12 to 17 years in the naproxen treatment group, 20 received a total daily dose of 750 mg naproxen, the dose prescribed for patients less than or equal to 60 kg, 11 received 1000 mg, the dose prescribed for patients greater than 60 kg, and 1, AN 537, received a dose of 500 mg for the entire open label extension.

Mean Duration

In the **12-week study**, the mean duration of exposure in **2 year to 11 year old patients** was 81.6, 82.3, and 80.6 days in the lower dose rofecoxib, higher dose rofecoxib and naproxen treatment groups, respectively. The mean duration of exposure in **12 to 17 year old patients** was 82.2, 84.7, and 79.2 days in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively.

In the **52-week open-label extension,** the mean duration of exposure in **2 year to 11 year old patients** was 331.6 and 295.9 days for the rofecoxib and naproxen treatment

groups, respectively. The mean duration of exposure in **12 year to 17 year old patients** was 346.5 and 292.4 days in the rofecoxib and naproxen treatment groups, respectively.

Deaths

No patients died during the 12-week study or during the 52-week open-label extension study.

Serious Adverse Events

There were 23 SAE during the study program. In the **12-week study**, serious adverse events (SAE) occurred in 5 patients: 2 patients in the lower-dose rofecoxib group, 2 patients in the higher-dose rofecoxib group and 1patient in the naproxen group. See **Table 26.**

T**able 26. 12-Week Study,** Protocol 134/135, Patients with Serious Adverse Events (This (Table is partially from the sponsor's Table 50, Section 8.2, page 152 of 2398)

Patient #, Age, Gender	**Study Drug, dosage**	**Serious AE, day of onset; concomitant medications**	**Outcome**
AN 552, 14 yrs, Male	Lower-dose rofecoxib, 12.5 mg	Worsening JRA, Still's disease; day 7; concomitant meds: MTX, diclofenac and acetaminophen	Hospitalization; Rx diclofenac, prednisone, naproxen and chloroquine were started; d/c home
AN 168, 11 yrs, Female	Higher-dose rofecoxib, 0.6 mg/kg	Worsening polyarticular JRA; day 119 (13 days after completing the study/stopping study medication; concomitant meds: AZA, vitamin E	Hospitalization on day (b) (6) injection of triamcinolone hexacetomide day (b) (6) recovered, d/c home
AN 634, 9 yrs, Male	Higher-dose rofecoxib, 0.6 mg/kg	Worsening JRA; day 93; Diagnosed uveitis; hospitalization day (b) (6); concomitant meds: MTX	Completed study medication; multiple joint injections; Rx naproxen; increased MTX dose from 10mg/kg/wk to 15mg/kg/wk; recovered day (b) (6) d/c home
AN 116, 6 yrs, Female	15mg/kg, naproxen	Worsening JRA, gastroenteritis, lymphadenopathy, intermittent fever, anemia; central-venous catherization	
AN 552, 14 yrs., Male	Lower-dose rofecoxib	Worsening JRA	Hospitalized required; discontinued study medication

Note: patient AN 552, a 14-year old boy with a history of Still's disease, discontinued study mediation (lower-dose rofecoxib) on day 7 due to worsening of JRA. This teen suffered worsening disease with worsening limited range of motion and specific right hip pain on motion during randomization into the protocol and later required hospitalization

by day (b) (6) The reviewer questions if this patient should have been included in this trial by subset definition and duration of diagnosis/remission.

In the **52-week open-label extension**, serious clinical adverse experiences occurred in 17 (7.5%) of 227 patients. See **Table 27.** Serious clinical adverse experiences occurred in 10(6.3%) and 7(10.4%) patients in the rofecoxib and naproxen treatment groups, respectively. None of the serious adverse experiences were determined by the investigator to be drug related. Two of the serious adverse experiences resulted in patient discontinuation of study medication. See **Table 28** for details of patient AN 200 and AN 199.

- Patient AN 200 (higher-dose rofecoxib) was discontinued from study due to hepatitis A.
- Patient AN 199 (naproxen) was discontinued from study due to worsened JRA.

Withdrawals/Discontinuations

In the **12-week study**, 5 patients discontinued due to adverse events: 3 (3.0%) treated with low-dose rofecoxib and 2 (2.0%) treated with naproxen group.

Low-dose rofecoxib group

- Patient AN 253, 10-year old male, and Patient AN 636, 3-year old female, discontinued lower-dose rofecoxib due **abdominal pain** which was determined by the investigator to be study-drug related. Patient AN 253 had onset of epigastric discomfort, intermittent vomiting day 11 to 38, and hyperopia, abdominal pain specifically on day 31, medication was continued until day 39; this patient also had diarrhea on day 39 and 40 which the investigator believed was study drug related.
- Patient AN 636 had onset of **abdominal pain** on day 11, medication was continued until day 39.
- Patient AN 552*, a 14-year old male, taking lower-dose rofecoxib, discontinued due to **worsening of juvenile rheumatoid arthritis**, which was determined by the investigator to be non-study-drug related. The flare of JRA occurred at 7 days of study drug therapy.

Naproxen group

- Patient AN 391, 14-year old female, discontinued (naproxen) due to a **migraine headache** which was determined by the investigator to be related to study drug. She had a history of migraine headaches, hypermobility syndrome, lactose intolerance, gastroesophageal reflux disease. She also had a rash on day 17, believed not to be study drug related, mouth ulcers on day 7 to 10, not study drug related, and abdominal pain on day 13 to 20, possibly study drug related. The adverse experience of the migraine headache resulted in discontinuation of the study drug.
- Patient AN 475, 16-year old female, was taking naproxen and discontinued due to **hematochezia**, which the investigator determined to be related to study drug. She suffered headache on day 3 to 10, left upper abdominal pain on day 4 to 10, hematochezia on day 6 to 10 and later reported multiple episodes of red blood in

her stool. Her hemoglobin at baseline was 12.8 gm/dl and 12.5 gm/dl day 17; her hematocrit at baseline was 37% and on day 17 was 36.3%.

The use of NSAIDs and non-selective COX-2 inhibitors in adult RA can be associated with adverse events including GI bleeding, renal effects, hepatic effects and allergic reactions. In the **52-week extension**, discontinuation rates due to adverse events were lower in the rofecoxib treatment group than in the naproxen treatment group, 3.8% and 11.9%, respectively.

Table 27. 52-Week Open-Label Extension, Protocol 134/135, Adverse Events Summary (Taken from the sponsor's submission, Table 49, Section 8.2, page 140)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	119	(74.4)	52	(77.6)
With no adverse experience	41	(25.6)	15	(22.4)
With drug-related adverse experiences†	19	(11.9)	13	(19.4)
With serious adverse experiences	10	(6.3)	7	(10.4)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued from therapy due to adverse experiences	4	(2.5)	8	(11.9)
Discontinued from therapy due to drug-related adverse experiences	2	(1.3)	5	(7.5)
Discontinued from therapy due to serious adverse experiences	1	(0.6)	1	(1.5)
Discontinued from therapy due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.

Twelve patients discontinued in the 52-week open-label extension due to adverse events: 4 patients (2.5%) in the rofecoxib treatment group and 8 patients (11.9%) in the naproxen treatment group. Of the 4 patients in the rofecoxib treatment group, two patients discontinued due to GI disorders, upper abdominal pain and gastritis, one patient discontinued for alopecia, and one patient discontinued due hepatitis A. Five of 8 patients in the naproxen treatment group discontinued for adverse events of the GI disorders (GI upset, GI pain, upper abdominal pain, abdominal pain, and constipation), 2 patients discontinued for worsening of JRA, and 1 patient discontinued for hepatitis A.

Table 28. 52-Week Open-Label Extension, Protocol 134/135, Withdrawals Due to Clinical Adverse Experiences (Taken, in part from the sponsor's submission, Table 52, Section 8.2, page 147)

Pt. AN #, Age, Sex	**Therapy and Dose**	**Relative Days at onset**	**Averse Experience**	**Action Taken**	**Outcome**
Assigned Therapy: Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg					
# 115, 9 yr, F	Rofecoxib, 17.5 mg	289	Alopecia, moderate	Rx D/C	Not recovered
# 200, 7 yrs., F	Rofecoxib, 14.5 mg	322	Hepatitis A, severe	Rx D/C	Recovered
# 622, 4 yrs., F	Rofecoxib, 9.6 mg	235	Abdominal pain, mild	Rx D/C	Recovered

#548, 12 yrs., F	Off drug x 3 days	376	Gastritis nos, moderate	Rx D/C	Recovered
Assigned Therapy: Naproxen 15 mg/kg					
# 61, 6 yrs, F	Naproxen, 295 mg	188	Gastrointestinal pain, Nos; severe	Possibly	Recovered
# 99, F, 9 yrs.	Naproxen, 420 mg	138	Constipation; mild	Possibly	Not Recovered
# 199, M, 4 yrs.	Naproxen, 275 mg	428	JRA; severe	Probably not	Recovered
# 244, F, 6 yrs.	Naproxen, 300 mg	276	Hepatitis A; moderate	Definitely not	Recovered
# 247, F, 7 yrs.	Naproxen, 470 mg	201	JRA; moderate	Definitely not	Recovered
# 294, F, 9 yrs.	Off drug 1 day, N/A	334	Abdominal pain, upper; moderate	Probably	Recovered
# 324, F, 14 yrs.	Naproxen, 1000 mg	103	Gastrointestinal upset; moderate	Probably	Recovered
# 558, M, 16 yrs.	Naproxen, 1000 mg	87	Abdominal pain nos; moderate	Probably	Recovered
Nos - No other symptoms; F - Female; M - Male					

In the **52-week extension**, the incidence of patients who discontinued due to GI adverse events was lower in the rofecoxib treatment group. According to the sponsor, based on an evaluation of 95% CI, the between-group difference of -6.2% was significant (rofecoxib versus naproxen; 95% CI [-15.1, -0.9%]). Two (1.3%) patients in the rofecoxib treatment group and 5 (7.5%) patients in the naproxen treatment group discontinued study drug due to gastrointestinal adverse experiences. Of the 2 patients who discontinued in the rofecoxib treatment group, 1 was due to an adverse experience of upper abdominal pain, and 1 was due to gastritis. Of the 5 patients in the naproxen treatment group, each had one GI adverse event as abdominal pain, upper abdominal pain, constipation, GI pain and GI upset. See **Table 29** and **30.**

Table 29. 52-Week Extension Study, Protocol 134/135, Prespecified Analysis of Number (%) of patients with GI Adverse Events
(This table is from the sponsor's submission, Table 60, Section 8.4, page 171 of 2044)

Patients With 1 or More Gastrointestinal Adverse Experiences			
Treatment Group	Proportion	Percent	
Higher-Dose Rofecoxib Naproxen	44/ 160 26/ 67	27.5% 38.8%	
Comparison Between Treatment Groups	Differences in Percentage Points	95% C.I. on Treatment Differences	p-Value†
Higher-Dose Rofecoxib vs. Naproxen	-11.3%	(-24.8, 1.7)	0.115
Patients Discontinued for Gastrointestinal Adverse Experiences			
Higher-Dose Rofecoxib Naproxen	2/160 5/67	1.3% 7.5%	
Comparison Between Treatment Groups	Differences in Percentage Points	95% C.I. on Treatment Differences	p-Value†
Higher-Dose vs. Naproxen	-6.2%	(-15.1, -0.9)	0.025
† p-value are provided only for those prespecified Adverse Experiences defined in the Data Analysis Plan.			

Table 30. 52-Week Extension Study, Protocol 134/135, Number (%) of Patients with Specific Clinical Adverse Events Discontinued Due to Gastrointestinal Disorders
(Table 62 is from the sponsor's submission, Table 62, Section 8.4.2.2, page 174 of 2398.)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)	
	n	(%)	n	(%)
Patients with one or more adverse experience	2	(1.3)	5	(7.5)
Patients with no adverse experience	158	(98.8)	62	(92.5)
Gastrointestinal Disorders	**2**	**(1.2)**	**5**	**(7.5)**
Abdominal Pain Nos	0	(0.0)	1	(1.5)
Abdominal Pain Upper	1	(0.6)	1	(1.5)
Constipation	0	(0.0)	1	(1.5)
Gastritis Nos	1	(0.6)	0	(0.0)
Gastrointestinal Pain Nos	0	(0.0)	1	(1.5)
Gastrointestinal Upset	0	(0.0)	1	(1.5)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. NOS=No Other Symptoms.				

Non-Serious Adverse Events

12-Week Study

From the combined study base, 196 (63.2%) of 310 JRA patients were noted to have adverse events as shown in **Table 31.** One or more clinical adverse events were: 72 patients (66.1%), 61 patients (61.0%) and 63 patients (62.4%), lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. As reported by the sponsor, drug-related (determined by the investigator to be possibly, probably, or definitely drug related) clinical adverse experiences were 21 patients (19.3%), 22 patients (22.0%) and 28 patients (27.7%), lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively.

Table 31. 12-Week Study, Protocol 134/135, Adverse Events Summary
(Table is from the sponsor's submission, Section 8.2, Table 45, page 140)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
with one or more adverse experiences	72	(66.1)	61	(61.0)	63	(62.4)
with no adverse experience	37	(33.9)	39	(39.0)	38	(37.6)
with drug-related adverse experiences†	21	(19.3)	22	(22.0)	28	(27.7)
with serious adverse experiences	1	(0.9)	2	(2.0)	1	(1.0)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to adverse experiences	3	(2.8)	0	(0.0)	2	(2.0)
discontinued due to drug-related adverse experiences	2	(1.8)	0	(0.0)	2	(2.0)
discontinued due to serious adverse experiences	1	(0.9)	0	(0.0)	0	(0.0)
discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.

In the **12-week study**, only adverse events occurring ≥ 3% of patients in any treatment group are presented in **Table 32**; however, this Reviewer presents pertinent findings from all adverse event reporting. Adverse events were more frequent in the gastro-intestinal disorders, infections and respiratory, thoracic and mediastinal disorders systems. In order of decreasing frequency, the three most commonly reported individual adverse events were abdominal pain, upper abdominal pain and headache.

Gastrointestinal disorders affected 29 (26.6%), 32 (32.0%) and 40 (39.6%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. **Abdominal pain** was noted in 7 (6.4%), 6 (6.0%) and 13 (12.9%) patients in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen groups, respectively. **Upper abdominal pain** occurred as 7 (6.4%), 12 (12.0%) and 7 (6.9%) of patients treated with low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Diarrhea was noted as 5(4.6%), 7(7.0%) and 4 (4.0%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Nausea was more prominent in the naproxen treated group, 3 (2.8%), 4 (4.0%) and 6 (5.9%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Vomiting, not otherwise specified, was noted as 7 (6.4%), 3 (3.0%) and 3 (3.0%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively.

Headache was the third most commonly reported adverse experience occurring in 6 (5.5%), 5 (5.0%) and 13 (12.9%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Headache was more prominent in the naproxen treated group than either study drug group and is a well-known adverse event with naproxen and other NSAIDs.

Upper respiratory tract infection demonstrated an incidence of 6 (5.5%), 6 (6.0%) and 7 (6.9%) with low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Respiratory, thoracic and mediastinal disorders, demonstrated 27 (24.8%) 24 (24.0%) and 11 (10.9%) incidence with low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Within the system grouping of respiratory, thoracic and mediastinal disorders, nasopharyngitis was noted in 11 (10.1%), 10 (10.0%) and 1 (1.0%) patients and pharyngitis was noted in 7 (6.4%), 3 (3.0%) and 3(3.0%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. The lower rate of adverse experiences in the

naproxen treated group was attributed, by the sponsor, to a significantly lower rate of nasopharngitis as compared to the combined rofecoxib treated groups. This Medical Reviewer agrees with the sponsor in that the incidence of adverse experiences in the respiratory, thoracic and mediastinal disorders system was representative of the incidence of these disorders in the prior history of these pediatric patients.

In the **12-week study**, from the complete adverse experience data reported as ≥ 0.0 % incidence, additional adverse experiences of **pyrexia, musculoskeletal pain** and **insomnia**. **Pyrexia** was noted in 5 (4.6%), 4 (4.0%) and 9 (8.9%) of patients in the low-dose rofecoxib, high-dose rofecoxib and naproxen treated groups. Though the naproxen treated group had a lower incidence of respiratory infections and infestations often associated with pyrexia, the naproxen group had a higher incidence of pyrexia.

Musculoskeletal and connective tissue complications occurred in 2 patients (1.8%), 6 patients (6.0%) and 10 patients (9.9%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. **Back pain** was reported in 3 patients treated with naproxen; there were no reports of back pain in either rofecoxib treated group. **Psychiatric disorders** were noted in 3 (2.8%), 4(4.0%) and 1 (1.0%), low-dose rofecoxib, high-dose rofecoxib and naproxen respectively. **Insomnia**, a known adverse experience with NSAIDs and selective COX-2 inhibitors, was reported as 1 (1.0%), 3 (3.0%) and 1 (1.0%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively.

Skin and **subcutaneous tissue disorders** showed 9 (8.3%), 11 (11.0%) and 10 (9.9%), low-dose rofecoxib, high-dose rofecoxib and naproxen, respectively. Adverse events included eczema, exanthems, contusions and rash, as not otherwise specified. One case of **pseudoporphyria** was reported with higher-dose rofecoxib.

Table 32. 12-Week Study, Protocol 134/135, Number (%) of Patients with Specific Clinical Adverse Experiences (Incidence ≥ 3.0% in One or More Treatment Groups) by Body system (Table is from the sponsor's submission, Section 8.2, Table 47, page 144 of 2398)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experience	72	(66.1)	61	(61.0)	63	(62.4)
Patients with no adverse experience	37	(33.9)	39	(39.0)	38	(37.6)
Eye Disorders	**4**	**(3.7)**	**4**	**(4.0)**	**4**	**(4.0)**
Gastrointestinal Disorders	**29**	**(26.6)**	**32**	**(32.0)**	**40**	**(39.6)**
Abdominal Pain Nos	7	(6.4)	6	(6.0)	13	(12.9)
Abdominal Pain Upper	7	(6.4)	12	(12.0)	7	(6.9)
Diarrhea Nos	5	(4.6)	7	(7.0)	4	(4.0)
Dyspepsia	2	(1.8)	0	(0.0)	3	(3.0)
Gastritis Nos	2	(1.8)	2	(2.0)	3	(3.0)
Gastroenteritis Nos	5	(4.6)	3	(3.0)	2	(2.0)
Nausea	3	(2.8)	4	(4.0)	6	(5.9)
Vomiting Nos	7	(6.4)	3	(3.0)	3	(3.0)
General Disorders And Administration Site Conditions	**10**	**(9.2)**	**5**	**(5.0)**	**13**	**(12.9)**
Pyrexia	5	(4.6)	4	(4.0)	9	(8.9)
Infections And Infestations	**23**	**(21.1)**	**24**	**(24.0)**	**17**	**(16.8)**
Bronchitis Acute Nos	0	(0.0)	4	(4.0)	1	(1.0)
Impetigo Nos	0	(0.0)	3	(3.0)	0	(0.0)
Influenza	1	(0.9)	1	(1.0)	4	(4.0)
Otitis Media Nos	2	(1.8)	3	(3.0)	0	(0.0)
Upper Respiratory Tract Infection Nos	6	(5.5)	6	(6.0)	7	(6.9)
Injury, Poisoning And Procedural Complications	**3**	**(2.8)**	**7**	**(7.0)**	**6**	**(5.9)**
Injury Nos	0	(0.0)	3	(3.0)	0	(0.0)
Musculoskeletal And Connective Tissue Disorders	**2**	**(1.8)**	**6**	**(6.0)**	**10**	**(9.9)**
Back Pain	0	(0.0)	0	(0.0)	3	(3.0)
Nervous System Disorders	**7**	**(6.4)**	**8**	**(8.0)**	**17**	**(16.8)**
Headache	6	(5.5)	5	(5.0)	13	(12.9)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)	
	n	(%)	n	(%)	n	(%)
Psychiatric Disorders	**3**	**(2.8)**	**4**	**(4.0)**	**1**	**(1.0)**
Insomnia	1	(0.9)	3	(3.0)	1	(1.0)
Respiratory, Thoracic And Mediastinal Disorders	**27**	**(24.8)**	**24**	**(24.0)**	**11**	**(10.9)**
Bronchitis Nos	2	(1.8)	4	(4.0)	1	(1.0)
Cough	4	(3.7)	0	(0.0)	1	(1.0)
Nasopharyngitis	11	(10.1)	10	(10.0)	1	(1.0)
Pharyngitis	7	(6.4)	3	(3.0)	3	(3.0)
Rhinitis Nos	0	(0.0)	5	(5.0)	0	(0.0)
Skin And Subcutaneous Tissue Disorders	**9**	**(8.3)**	**11**	**(11.0)**	**10**	**(9.9)**

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Non-Serious Adverse Events

52-Week Extension

In the **52-week extension**, adverse events were reported in 171 (75.3%) of 227 patients in the combined open-label extension. One or more adverse events occurred in 119 (74.4%) and 52 (77.6%) patients in the rofecoxib and naproxen treatment groups, respectively. The most commonly reported adverse events were **headache, upper respiratory tract infection, nasopharyngitis** and **pharyngitis**. See **Table 33.** An adverse experience of upper respiratory infection was reported in 20 (12.5%) and 4 (6.0%) patients in the rofecoxib and naproxen treatment groups, respectively. **Nasopharyngitis** was reported in 11 (6.9%) and 9 (13.4%) patients in the rofecoxib and naproxen treatment groups. **Pharyngitis** was reported in 11 (6.9%) and 9 (13.4%) patients in the rofecoxib and naproxen treatment groups, respectively. None of these adverse experiences were determined by the investigator to be study-drug related and none resulted in discontinuation.

The most commonly reported adverse event of the gastrointestinal system was **upper abdominal pain** which was reported in 11 (6.9%) and 8 (11.9%) patients in the rofecoxib and naproxen treatment groups, respectively. The second most commonly reported adverse event of this system was **abdominal pain** which was reported in 10 (6.2%) and 4 (6.0%) patients in the rofecoxib and naproxen treatment groups, respectively.

Table 33. 52-Week Extension, Protocol 134/135, Number (%) of Patients with Specific Adverse Events by Body System, (Table is from the sponsor's Table 50, Section 8.2, pp 142-143)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)	
	n	(%)	n	(%)
Patients with one or more adverse experience	119	(74.4)	52	(77.6)
Patients with no adverse experience	41	(25.6)	15	(22.4)
Blood And Lymphatic System Disorders	**4**	**(2.5)**	**4**	**(6.0)**
Ear And Labyrinth Disorders	**1**	**(0.6)**	**2**	**(3.0)**
Ear Pain	1	(0.6)	2	(3.0)
Eye Disorders	**10**	**(6.2)**	**3**	**(4.5)**
Gastrointestinal Disorders	**44**	**(27.5)**	**26**	**(38.8)**
Abdominal Pain Nos	10	(6.2)	4	(6.0)
Abdominal Pain Upper	11	(6.9)	8	(11.9)
Constipation	2	(1.2)	3	(4.5)
Diarrhea Nos	3	(1.9)	6	(9.0)
Gastroenteritis Nos	9	(5.6)	2	(3.0)
Mouth Ulceration	5	(3.1)	2	(3.0)
Nausea	4	(2.5)	2	(3.0)
Vomiting Nos	6	(3.8)	3	(4.5)
General Disorders And Administration Site Conditions	**17**	**(10.6)**	**10**	**(14.9)**
Pyrexia	10	(6.2)	7	(10.4)
Infections And Infestations	**61**	**(38.1)**	**28**	**(41.8)**
Bronchitis Acute Nos	3	(1.9)	6	(9.0)
Ear Infection Nos	5	(3.1)	1	(1.5)
Helicobacter Gastritis	1	(0.6)	2	(3.0)
Hepatitis A	1	(0.6)	2	(3.0)
Herpes Simplex	0	(0.0)	2	(3.0)
Impetigo Nos	1	(0.6)	3	(4.5)
Influenza	5	(3.1)	0	(0.0)
Pharyngitis Streptococcal	5	(3.1)	0	(0.0)
Sinusitis Nos	5	(3.1)	0	(0.0)
Tonsillitis	4	(2.5)	3	(4.5)
Upper Respiratory Tract Infection Nos	20	(12.5)	4	(6.0)
Injury, Poisoning And Procedural Complications	**14**	**(8.8)**	**1**	**(1.5)**

(Table 33, Continued)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)	
	n	(%)	n	(%)
Musculoskeletal And Connective Tissue Disorders	**15**	**(9.4)**	**6**	**(9.0)**
Arthralgia	3	(1.9)	2	(3.0)
Juvenile Rheumatoid Arthritis	6	(3.8)	4	(6.0)
Nervous System Disorders	**26**	**(16.2)**	**9**	**(13.4)**
Headache	24	(15.0)	8	(11.9)
Psychiatric Disorders	**4**	**(2.5)**	**3**	**(4.5)**
Renal And Urinary Disorders	**3**	**(1.9)**	**2**	**(3.0)**
Reproductive System And Breast Disorders	**4**	**(2.5)**	**3**	**(4.5)**
Respiratory, Thoracic And Mediastinal Disorders	**30**	**(18.8)**	**21**	**(31.3)**
Bronchitis Nos	1	(0.6)	2	(3.0)
Cough	3	(1.9)	7	(10.4)
Nasopharyngitis	11	(6.9)	9	(13.4)
Pharyngitis	11	(6.9)	9	(13.4)
Skin And Subcutaneous Tissue Disorders	**16**	**(10.0)**	**8**	**(11.9)**
Although a patient may have had 2 or more clinical adverse experiences, the patient was counted only once within a category. The same patient may appear in different categories.				

According to the sponsor, drug-related (determined by the investigator to be possibly, probably, or definitely drug related) clinical adverse events occurred in 19 patients (11.9%) and 13 patients (19.4%) in the rofecoxib and naproxen treatment groups, respectively. Drug related adverse events occurred most frequently in the gastrointestinal system, in 11 patients (6.9%) and 11 patients (16.4%) in the rofecoxib and naproxen treatment groups, respectively.

Non-Serious Laboratory Adverse Events

12-Week Study

In the **12-week study**, the use of NSAIDs in the adult RA population can be associated with adverse effects including gastrointestinal bleeding, renal effects, hepatic effects and allergic reactions. Accordingly, parameters of prespecified concern were hemoglobin, hematocrit, aspartate aminotransferase (ALT), alanine aminotransferase (AST) and serum creatinine, the proportion of patients outside the predefined limits were compared between active treatments. There were no patients with laboratory adverse experience of increased serum creatinine. See **Table 34 and 35.**

Table 34. 12-Week Study, Summary of Laboratory Adverse Events
(This Table is from the sponsor's submission, Section 8.3, Table 51, page 156 of 2398)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)	
	n	(%)†	n	(%)†	n	(%)†
Number (%) of patients:						
With at least one laboratory test postbaseline	108		100		100	
With one or more adverse experiences	11	(10.2)	8	(8.0)	11	(11.0)
With no adverse experience	97	(89.8)	92	(92.0)	89	(89.0)
With drug-related adverse experiences‡	5	(4.6)	2	(2.0)	5	(5.0)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	3	(2.8)	1	(1.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	3	(2.8)	1	(1.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

† The percent = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.

Table 35. 12-Week Study, Protocol 134/135, Adverse Events by Laboratory Test and Treatment Group (Table is from the sponsor's submission, Table 53, Section 8.3, p 160)

	Rofecoxib 0.3 mg/kg or Rofecoxib 12.5 mg (N=109)		Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=100)		Naproxen 15 mg/kg (N=101)	
	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	11/108	(10.2)	8/100	(8.0)	11/100	(11.0)
Patients with no adverse experience	97/108	(89.8)	92/100	(92.0)	89/100	(89.0)
Blood Chemistry Test	**4/108**	**(3.7)**	**2/100**	**(2.0)**	**4/100**	**(4.0)**
Alanine Aminotransferase Increased	4/108	(3.7)	2/100	(2.0)	1/100	(1.0)
Aspartate Aminotransferase Increased	3/108	(2.8)	2/100	(2.0)	1/100	(1.0)
Blood Bicarbonate Decreased	0/108	(0.0)	0/100	(0.0)	1/100	(1.0)
Blood Glucose Decreased	0/108	(0.0)	0/100	(0.0)	1/100	(1.0)
Blood Phosphate Increased	0/108	(0.0)	0/100	(0.0)	1/100	(1.0)
Hematology Laboratory Test	**3/108**	**(2.8)**	**4/100**	**(4.0)**	**2/100**	**(2.0)**
Eosinophil Count Increased	0/108	(0.0)	0/100	(0.0)	1/100	(1.0)
Hematocrit Decreased	0/108	(0.0)	2/100	(2.0)	0/100	(0.0)
Hemoglobin Decreased	1/108	(0.9)	3/100	(3.0)	0/100	(0.0)
Platelet Count Decreased	0/108	(0.0)	1/100	(1.0)	1/100	(1.0)
Red Blood Cell Sedimentation Rate Increased	1/108	(0.9)	0/100	(0.0)	0/100	(0.0)
White Blood Cell Count Decreased	1/108	(0.9)	0/100	(0.0)	0/100	(0.0)
Stool Analysis	**0/2**	**(0.0)**	**0/2**	**(0.0)**	**1/1**	**(100.0)**
Parasite Stool Test Positive	0/1	(0.0)	0/†		1/1	(100.0)
Urinalysis Test	**4/108**	**(3.7)**	**3/99**	**(3.0)**	**5/100**	**(5.0)**
Blood Urine Present	1/108	(0.9)	0/99	(0.0)	0/100	(0.0)
Glucose Urine Present	1/108	(0.9)	0/99	(0.0)	0/100	(0.0)
Protein Urine Present	3/108	(2.8)	1/99	(1.0)	4/100	(4.0)
Red Blood Cells Urine Positive	1/108	(0.9)	0/99	(0.0)	1/100	(1.0)
Urine Leukocyte Esterase Positive	0/108	(0.0)	2/99	(2.0)	1/100	(1.0)
White Blood Cells Urine Positive	0/108	(0.0)	1/99	(1.0)	1/100	(1.0)

† There was no associated laboratory test or no patient for whom a laboratory test was recorded postbaseline.
n/m=number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Drug-related laboratory adverse events (determined by the investigator to be possibly, probably, or definitely related to study medication) occurred in 5 patients (4.6%), 2 patients (2.0%), and 5 patients (5.0%) patients in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. Three patients (2.8 %), 1 patient (1.0 %) and 0 patients (0 %) in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups respectively, discontinued due to laboratory adverse events.

PK Safety
In review of the four PK Protocols completed by MRL, **Protocol 105, 109, 110 and 228**, only Protocol 105 was long enough in duration (14 weeks) to offer safety data. There were no deaths or serious adverse events and no patient discontinued therapy due to an adverse event. One patient, receiving naproxen, had nausea considered to be possibly drug related by the investigator. The adverse event profile for rofecoxib in Protocol 105 was consistent with well-known risks from NSAIDs and selective COX-2 inhibitor therapy.

Hepatic Enzyme Adverse Events

12-Week Study
Hepatic enzymes were considered elevated as greater than three times the upper limit of normal (> 3xULN). Elevated liver function tests, as ALT and/or AST, were the most common adverse laboratory events. See **Table 36 and 37.** Four patients (3.7%), 2 patients (2.0%) and 2 patients (2.0%) patients had elevated hepatic enzymes, with lower-dose rofecoxib, higher-dose rofecoxib and naproxen groups, respectively. Of these 8 patients, 3 patients AN 3, AN 225 and AN 546, in the lower-dose rofecoxib treatment group, and 2 patients, AN 236 and AN 593, in the higher-dose rofecoxib treatment group, reported adverse experiences of both increased ALT and AST. Three patients (2.8%), 2 patients (2.0%) and 2 patients (2.0%) patients in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively, had liver function test abnormalities that were determined by the investigator to be study-drug related. Serum bilirubin remained within normal limits in each of these patients.

Table 36. 12-Week Study, Prespecified Analyses of Number (%) of Patients with Laboratory Adverse Events of Increased ALT and AST
(This Table is from the sponsor's submission Table, 52, Section 8.3, page 157-158 of 2398)

Alanine Aminotransferase Increased			
Treatment Group	Proportion†	Percent	
Lower-Dose Rofecoxib	4/ 108	3.7%	
Higher-Dose Rofecoxib	2/ 100	2.0%	
Naproxen	1/ 100	1.0%	
Comparison Between Treatment Groups	Differences in Percentage Points	95% CI for Treatment Differences	p-Value
Higher-Dose Rofecoxib vs. Naproxen	1.0%	(-3.7, 6.1)	1.000
Lower-Dose Rofecoxib vs. Naproxen	2.7%	(-2.3, 8.2)	0.371
Higher-Dose vs. Lower-Dose Rofecoxib	-1.7%	(-7.3, 3.8)	0.684
Aspartate Aminotransferase Increased			
Treatment Group	Proportion	Percent	
Lower-Dose Rofecoxib	3/ 108	2.8%	
Higher-Dose Rofecoxib	2/ 100	2.0%	
Naproxen	1/ 100	1.0%	
Comparison Between Treatment Groups	Differences in Percentage Points	95% CI for Treatment Differences	p-Value
Higher-Dose Rofecoxib vs. Naproxen	1.0%	(-3.7, 6.1)	1.000
Lower-Dose Rofecoxib vs. Naproxen	1.8%	(-3.0, 6.9)	0.622
Higher-Dose vs. Lower-Dose Rofecoxib	-0.8%	(-6.1, 4.5)	1.000
Discontinued Due to Laboratory AE of Increased Alanine Aminotransferase			
Treatment Group	Proportion	Percent	
Lower-Dose Rofecoxib	2/ 108	1.9%	
Higher-Dose Rofecoxib	0/ 100	0.0%	
Naproxen	0/ 101	0.0%	

Discontinued Due to Laboratory AE of Increased Alanine Aminotransferase (Cont.)			
Comparison Between Treatment Groups	Differences in Percentage Points	95% CI for Treatment Differences	p-Value‡
Higher-Dose Rofecoxib vs. Naproxen	0.0%	(-3.7, 3.7)	1.000
Lower-Dose Rofecoxib vs. Naproxen	1.9%	(-2.1, 6.5)	0.498
Higher-Dose vs. Lower-Dose Rofecoxib	-1.9%	(-6.5, 2.1)	0.498
Discontinued Due to laboratory AE of Increased Aspartate Aminotransferase			
Treatment Group	Proportion	Percent	
Lower-Dose Rofecoxib	1/ 108	0.9%	
Higher-Dose Rofecoxib	1/ 100	1.0%	
Naproxen	0/ 101	0.0%	
Comparison Between Treatment Groups	Differences in Percentage Points	95% CI for Treatment Differences	p-Value‡
Higher-Dose Rofecoxib vs. Naproxen	1.0%	(-2.8, 5.4)	0.498
Lower-Dose Rofecoxib vs. Naproxen	0.9%	(-2.8, 5.1)	1.000
Higher-Dose vs. Lower-Dose Rofecoxib	0.1%	(-4.1, 4.6)	1.000

† Proportion is the number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was reported during the treatment period.

‡ p-value are provided only for those prespecified Adverse Experiences defined in the Data Analysis Plan.

Table 37. 12-Week Study, Laboratory Test Results as Adverse Events
(Partial table content from the sponsor's submission, Table 54, section 8.3, page 162)

Pt w/ ≥ one AE	Rofecoxib 0.3mg/kg or Rofecoxib 12.5mg N=109	Rofecoxib 0.6mg/kg or Rofecoxib 25mg N=100	Naproxen 15 mg/kg N=101
ALT increased;	3/108 (2.8%);	2/100 (2.0%)	1/100 (1.0%)
AST increased	2/108 (1.9%)	2/100 (2.0%)	1/100 (1.0%)
Platelets increased	0/108 (0.0%)	0/100 (0.0%)	1/100 (1.0%)
UA Leukocyte Positive	0/108 (0.0%)	0/99 (0.0%)	1/100 (1.0%)
UA Protein Positive	2/108 (1.9%)	0/99 (0.0%)	2/100 (2.0%)

52-Week Extension
In the **52-week extension**, the incidence of adverse events of **increased ALT and/or AST** was as follows: 7 patients (4.4%) and 1 patient (1.5%) patients in the rofecoxib and naproxen treatment groups, respectively, reported increased ALT or increased AST. Two patients in the rofecoxib treatment group **discontinued** due to increased ALT or increased AST. One of the adverse events was determined by the investigator to be possibly related to study drug. Six patients, 4 patients (2.6%) rofecoxib, 2 patients (3.1%) naproxen treatment group, were identified as having one or more values greater than three times the upper limit of normal (ULN), if normal at baseline, for serum ALT. Five of these patients, 3 patients (2.0%) treated with rofecoxib, 2 patients (3.1%) treated with naproxen, also had 1 or more values greater than 3 times the upper limit of normal (if normal at baseline) for serum AST.

Withdrawals/Discontinuations Due to Laboratory Adverse Events

12-Week Study
In the **12-week study**, three patients in the lower dose rofecoxib treatment group and 1 patient in the higher-dose rofecoxib treatment group discontinued study drug due to liver function-test-related adverse events. Three patients AN 3, AN 546 and AN 236 were identified as having one or more values greater than three times the upper limits of normal (if normal at baseline) for serum ALT and/or AST. All three patients were discontinued from study therapy for an associated laboratory adverse event. See **Table 38.**

Table 38. 12-Week Study, Patients Discontinued due to Laboratory Adverse Events
(This table has partial content from the sponsor's Table 55, Section 8.3, page 164 of 2398)

Patient #, Age, Gender	Study Drug Dosage	Lab Adverse Event	Outcome
AN 3, 11 yrs, Male	Rofecoxib 12.5mg (0.3mg/kg) (+ MTX, Embrel, ferrous sulfate, folic acid, calcium)	AST 18 - 78 mlU/mL; ALT 17 -126 mlU/mL	Probably Drug Related; Rx D/C
AN 24, 6 yrs, Female	Rofecoxib 5.17mg (0.3mg/kg) (+ Senna)	AST 27 - 38 ml U/mL ALT 12 - 45 mlU/mL Bilirubin 0.35 - 0.55mg/dl	Definitely; Rx D/C
AN 546, 15 yrs, Male	Rofecoxib 12.5mg (+ MTX, calcium, folic acid, calcium)	AST 19 - 119 mlU/mL ALT 13 - 137 mlU/mL Bilirubin 0.54 - 1.03 mg/dl	Possibly, Rx D/C
AN 236, 7 yrs, Female	Rofecoxib 14.0mg (0.6mg/kg) (+ MTX)	AST 23 - 175 mlU/mL ALT 18 - 282 mlU/mL	Possibly, Rx D/C/

Bilirubin = Serum bilirubin normal ranges 0.1 to 1.1mg/dl; MTX = Methotrexate

Withdrawals/Discontinuations

52-Week Extension

In the **52-week extension**, two patients in the rofecoxib treatment group discontinued study drug due to laboratory adverse events of increased ALT and increased AST; and one patient in the naproxen group had elevated hepatic enzymes with jaundice and was diagnosed with hepatitis A. This patient's study medication was interrupted twice; however, this patient completed the 52-week extension. See **Table 39.**

Table 39. 52-Week Extension, Patients Discontinued Due to Laboratory Adverse Events
(Portions of this Table are from the sponsor's Table 59, Section 8.3, page 169 of 2044)

AN Patient/ Gender/Age	Adverse Event	Relative day of onset	Drug Relationship	Action Taken
Rofecoxib 0.6mg/kg/day or Rofecoxib 25mg per day				
AN 78, F, 4 yrs. old	Increased ALT	456	Possible	Rx D/C
AN 78, F, 4 yrs. old	Increased AST	456	Possible	Rx D/C
AN 246, M, 10 yrs. old	Increased ALT	260	Possible, Probably not	Rx D/C
AN 246, M, 10 yrs. old	Increased AST	260	Possible, Probably not	Rx D/C
Naproxen 15mg/kg/day				
An 235, F, 5 yrs. old	Increased ALT*	176; Jaundice Day 179-197	Possible	Continued w/interruptions

An 235, F, 5 yrs. old	Increase AST*	176; Jaundice Day 179-197	Possible	Continued w/interruptions
*Elevated Bilirubin w/jaundice was reported in this patient; Hepatitis A positive; Hepatitis B negative.				

Other Adverse Events of Special Interest

Allergic Skin Reactions
In the **12-week study**, there were no serious adverse events of allergic-type skin or hypersensitivity reactions. One patient in the higher-dose rofecoxib treatment group had three mild adverse events of exanthem, lasting 8 hours. One patient in the naproxen treatment group had a mild adverse event of rash that lasted 12 hours. All of these adverse events resolved, and none resulted in the discontinuation of study medication.

In the **52-week extension**, there was one patient in which pseudoporphyria was reported with rofecoxib.

Cardiorenal
Adverse events of edema, hypertension, congestive heart failure and renal insufficiency have been associated with the use of NSAIDs and selective COX-2 inhibitors in adults. In **12-week study,** an adverse experience of peripheral edema as edema of the ankles and feet, was reported in 1 (1.0%) patient in the higher-dose rofecoxib treatment group. The patient's medical history included increased serum creatinine of 1.2 mg/dL at baseline (normal range 0.6 to 1.2 mg/dL) and increase to 1.4 mg/dL on Day 95. Con-concomitant medications included ambroxol and rescue acetaminophen. The patient's weight was 46.2 kg (baseline) and 48.5 kg by Day 56. No treatment was required and the patient completed the study and enrolled in the extension.

In **52-week extension,** there were no clinical adverse events of hypertension, congestive heart failure, or renal insufficiency in patients in either treatment group. One patient in the rofecoxib treatment group developed acute post-streptococcal glomerulonephritis. Three adverse events consistent with edema were reported; however, this Medical Reviewer finds only one of these three events is probably a drug related.

Central Nervous System
In the **12-week study**, one patient (0.9%), two patients (2.0%) and one patient (1.0%) in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively, had adverse events of the central nervous system identified as dizziness and somnolence. One (1.0%) patient in the naproxen treatment group had somnolence. None of the patients discontinued study drug. Headaches were noted in all three treatment groups and were reported in the non-serious adverse event section of this review.

In the **52-week extension**, two patients in the rofecoxib treatment group reported dizziness. One patient, four years of age, in the naproxen treatment group reported convulsions without fever or infection. A CAT scan of his brain was negative and an

electroencephalogram showed disorganization of the tracing and low voltage in the right hemisphere. This patient was discharged from the hospital without any neurologic sequelae. This Medical Reviewer does not find this event to be drug related.

Uveitis
In the **12-week study**, uveitis, specifically, anterior uveitis, occurred in two (1.8%), one (1.0%) and one (1.0%) of patients, in the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, respectively. None of the patients with uveitis were discontinued the study and none were considered to be drug related by this Reviewer.

In the **52-week extension**, uveitis was reported in 2 patients in the rofecoxib treatment group. Each of these patients had a prior history of uveitis. This Medical Reviewer does not find either case of uveitis to be study drug related.

Growth and Development
In the **12-week study**, a single adverse experience of decreased weight on Day 85 occurred in a 16-year-old girl taking naproxen. The patient's weight change was less than 1 kg and this Medical Reviewer does not consider this to be study drug related.

In the **52-week extension**, there was one patient who developed premature thelarche; this Medical Reviewer does not consider this event to be study drug related.

Lymphadenopathy
In the **12-week study**, a 9 year old girl, taking 0.3 mg/kg, lower-dose rofecoxib, had lymphadenopathy on Day 79 which resolved on Day 85. The patient did not have a prior history of lymphadenopathy and this event was not considered study rug related.

In the **52-week extension**, one patient in each study group, rofecoxib and naproxen, respectively, developed lymphadenopathy. Neither was considered to be study drug related and nether required discontinuation from the study.

CONCLUSIONS, Integrated Review of Safety

In these two clinical studies, the most common adverse events were gastrointestinal signs and symptoms, headache and upper respiratory tract infections. The overall adverse event profile was consistent with known adverse events from NSAIDs and selective COX-2 inhibitors. In the **12-week study**, there were no clinically significant differences in the percentages of patients across treatment groups with one or more clinical adverse events or patients who discontinued due to an adverse event. Drug-related clinical adverse events were higher in the naproxen treatment group. The most common adverse events noted in the 12-week study were gastrointestinal disorders documented as abdominal pain, upper abdominal pain, diarrhea and nausea, followed by headache and upper respiratory tract infection. There was a higher incidence of abdominal pain in the naproxen treated group, 13 patients (12.9%), compared to the lower-dose of rofecoxib, 7 patients (6.4%), and higher-dose of rofecoxib, 6 patients (6.0%). The incidence of gastrointestinal adverse events was numerically higher in the naproxen treated group, due

to abdominal pain not otherwise specified; however, the incidence of gastrointestinal adverse events was similar across all three treatment groups, without statistical significance. Headache was more prominent in the naproxen treated group than either of the rofecoxib treated groups. The incidence of respiratory infections was representative of the prior history of the study patients. Less commonly reported adverse events were pyrexia and insomnia, both conditions occurred in all three treatment groups without statistical significance.

There were four serous adverse events, all of which were flares of JRA patient's polyarticular disease and not considered study drug related. Five patients withdrew due to clinical adverse events: two patients treated with low-dose rofecoxib suffered abdominal pain and one patient suffered worsening JRA; one teenager treated with naproxen suffered headaches and one teen treated with naproxen suffered hematochezia. No patients treated with high-dose rofecoxib suffered serious clinical adverse events.

The most common laboratory adverse event in the 12-week study and 52-week extension were elevated hepatic enzymes greater than 3 x ULN. Less common laboratory adverse events were elevated platelet count, and abnormal urinalysis with protein. Two adverse events related to cardiorenal systems, specifically, edema, were reported; however, only one of the two events was considered study-drug related. One patient treated with higher-dose rofecoxib suffered edema of the feet and ankles. There were mild to moderate allergic skin/hypersensitivity reactions across all three treatment groups.

The overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of rofecoxib and naproxen. The safety profile for rofecoxib in pediatric patients, as in adults, warrants careful monitoring of clinical signs and symptoms and laboratory tests. Hepatotoxicity is a specific risk and appears to be increased in patients treated with rofecoxib in addition to concomitant medications. The 52-week extension study and the efficacy data from the three small pediatric PK studies support the safety findings and conclusions from the 12-week study.

7.1.1.1 Additional Analyses and Explorations

Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. You should discuss the rationale for additional explorations, the methods used, and the results and interpretations.

7.1.1.2 Special Assessments

Gastrointestinal, hepatotoxicity, cardiorenal and allergic skin/hypersensitivity adverse events were assessed separately. See Section 7.1. Integrated Safety Review

7.1.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in these two pediatric clinical trials.

7.1.3 Overdose Experience

There were no significant overdoses in these two pediatric clinical trials.

7.1.4 Post-marketing Experience

Post marketing experience submitted is consistent with the adverse event profile of rofecoxib. A review of the post-marketing data was not part of this review.

7.1.5 Adequacy of Patient Exposure and Safety Assessments

Adequacy of drug exposure and the safety evaluations performed as part of the development program are presented in Section 7.1.

7.1.5.1 Adequacy of Overall Clinical Experience

There were a sufficient number of pediatric patients exposed to treatment by dose, age group and JRA subtype in the 12 week study with the 52-week extension. There were an imbalanced number of pediatric patients in the 52-week extension. Safety was assessed in these two clinical studies as well as from the three PK studies in JRA patients. Recruitment of JRA patients is challenging, particularly, in the younger age group. Placebo-controlled trials in pediatric rheumatology are not ethically possible as there are approved NSAIDs with the indication of relief of the signs and symptoms of JRA. Superiority or non-inferiority trial design is an option for the investigation of drugs for indications in pediatric patients. The design of these two clinical trials was non-inferiority and was acceptable to the Medical Reviewer.

7.1.6 Adequacy of Special Animal and/or In vitro Testing

Not applicable in these pediatric supplement reviews.

7.1.7 Adequacy of Routine Clinical Testing

The two clinical studies submitted are adequate for routine clinical monitoring and laboratory testing of pediatric patients, ≥ 2 years to ≤ 17 years of age, to elicit adverse event data. The frequency of testing in these pediatric and adolescent patients was adequate. See Section 7.1.

7.1.8 Adequacy of Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review by Lei K. Zhang, PHD and Jenny J. Zheng, PhD.
See Pharmacology Toxicology review by Josie Yang, PhD.

7.1.9 Assessment of Quality and Completeness of Data

These two clinical studies utilized quality control and assurance systems. The studies were conducted and data generated, documented, and reported, in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of clinical studies.

7.1.10 Summary of Selected Drug-Related Adverse Events

The most common adverse events from rofecoxib treatment were gastrointestinal disorders, as abdominal pain and upper abdominal pain, headache and upper respiratory tract infection. Less commonly noted were insomnia and pyrexia. The most common laboratory adverse event was elevated liver function tests without elevated serum bilirubin. Pediatric patients taking concomitant medications, specifically, methotrexate, appear to be at greater risk for elevated liver function tests than patients not taking concomitant DMARD medications. See Section 7.1 Integrated Review of Safety.

7.1.11 Safety Conclusions

Rofecoxib is safe for use in JRA patients at the approved dose of 0.6mg/kg per day to a maximum dose of 25 mg per day, who weigh less than or equal to 42 kg. In JRA patients who weigh greater than 42 kg, the recommended dose is 25 mg per day, maximum dose 25 mg per day. Careful clinical and laboratory monitoring must be used in prescribing rofecoxib to JRA patients, ≥2 years to ≤17 years of age. A starting dose of 0.3mg/kg per day is recommended, increased to a therapeutic dose of 0.6mg/k per day, maximum dose of 25 mg per day. See Section 7.0 and 7.1, Integrated Review of Safety. The safety profile of rofecoxib is comparable to naproxen and NSAID/selective COX-1/COX-2 inhibitor profiles. The safety of rofecoxib in children with body weight less than 10 kg has not been studied. In addition, rofecoxib has not been studied in the JRA subtype, systemic JRA.

8 ADDITIONAL CLINICAL ISSUES

8.1.1 Dosing Regimen and Administration

See Section 1.3, 1.1.7 Dosing Regimen and Administration. The medical review recommends consideration of study of rofecoxib in pediatric patients < 2 years of age and less than 10 kg. See Clinical Pharmacology review, Section 5, by Lei K. Zhang, PhD and Jenny J. Zheng, PhD, for dose response data and pharmacology parameters. See Section 6, Integrated Review of Efficacy.

8.1.2 Drug-Drug Interactions

Clinical trials in pediatric patients with JRA must account for concomitant medications commonly used in pediatric rheumatology patients such as NSAIDs, DMARDs and cytotoxic medication. The inclusion and exclusion criteria included highest risk concomitant medication in the trial design. Caution should be used with concomitant medications such as gold, methotrexate, sulfasalzine, anti-malarials and steroids because

the adverse event profiles are similar and concomitant medication may precipitate adverse experiences.

Heptatotoxicity is a well known risk with anti-rheumatic therapy, NSAIDs and DMARDs and must be considered with rofecoxib therapy as well as concomitant therapy and drug metabolism. It is important to note that the majority of these study patients who suffered elevated liver function tests were taking concomitant mediations with adverse event profiles including hepatotoxicity. Methotrexate, in particular, was a common concomitant medication among these study patients.

8.1.3 Special Populations

Prescribing rofecoxib should be managed cautiously in pediatric patients taking concomitant medications such as NSAIDs and DMARDs, patients under 2 years of age or with body weight less than 10 kg, children or adolescents with renal impairment or hepatic insufficiency and in those with allergic skin or hypersensitivity reactions. Pregnancy and lactation are both contraindications to treatment with rofecoxib.

8.1.4 Pediatrics

The efficacy and safety clinical trial Protocol 134/135 represents the largest clinical study of a NSAID/selective COX-1/COX-2 inhibitor, to date, in pediatric rheumatology patients, pauciarticular and polyarticular course. The study did not include systemic JRA course due to safety concerns of intravascular coagulopathy that are documented with NSAID therapy. In addition, the study did not include children smaller than 10 kg in body weight. See Section 1.3.1 Brief Overview of clinical Program and Section 2.5 Pre-Summary of the Regulatory Activity for additional pediatric specific information.

8.1.5 Advisory Committee Meeting

There was no Advisory Committee Meeting associated with these two NDA Pediatric Supplement Reviews.

8.1.6 Literature Review

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

8.1.7 Other Relevant Materials

There were no other relevant materials reviewed beyond the pediatric supplement documents and literature cited in the review.

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

The [redacted] 0.6mg/kg/day to a maximum dose of 25mg once per day, for relief of the signs and symptoms of pauciarticular or polyarticular type Juvenile Rheumatoid Arthritis (JRA) in pediatric patients 2 years to 17 years of age, demonstrated efficacy at the Division's recommended lower limit of the point estimate ≥ 0.75 margin for a non-inferiority trial. [redacted]

Within the non-inferiority study design of these two clinical trials, 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, regardless of completion status, over the 12-week base study were [redacted], 54.5 and 55.1% in [redacted] higher-dose rofecoxib and naproxen treatment groups, respectively.

There were no pediatric patients studied with body weight less than 10 kg. In patients with body weight greater than or equal to 10 kg, the pharmacokinetic profile demonstrated that the higher-dose rofecoxib produced exposure slightly less than the exposure produced in adult rheumatoid arthritis patients and slightly greater than the exposure produced in healthy adults.

The rofecoxib safety profile in pediatric patients with JRA is consistent with NSAID and selective COX-1/COX-2 inhibitor adverse event profiles. Rofecoxib treatment in pediatric patients requires very careful monitoring for safety and adverse events, specifically, for gastro-intestinal upset, as abdominal pain, headaches and upper respiratory tract infections. Pediatric patients treated with rofecoxib are at increased risk of adverse laboratory events, specifically, increased liver function test results. Pediatric patients appear to be at greater risk for if they are concurrently taking DMARDs, particularly, methotrexate. Caution must be used when prescribing rofecoxib with concomitant medications.

9.2 Recommendation on Regulatory Action

- Approval of the higher of two rofecoxib study doses, 0.6mg/kg/day to a maximum dose of 25mg once per day, suspension or tablet formulation, for relief of the signs and symptoms of pauciarticular and polyarticular course JRA in patients ≥ 2 years to ≤ 17 years of age, demonstrated efficacy in Protocol 134/135.
- [redacted]

- The label reflects the safety risks as demonstrated in these two clinical trials and four PK studies.

9.3 Recommendation on Post-Marketing Actions

No additional post-marketing risk management activities are recommended. The sponsor is requested to continue to report all adverse events and report all emergency adverse events within 15 days according to the FDA regulations.

9.3.1 Risk Management Activity

See Section 9.3

9.3.2 Required Phase 4 Commitments

Phase IV recommendations are as follows: study rofecoxib suspension in JRA patients, less than 10 kg in body weight and/or less than 2 years of age, with pauciarticular or polyarticular JRA; study rofecoxib in pediatric patients 2 years to 17 years of age with systemic JRA, including the additional safety monitoring recommended by the Division in the amended WR. This Medical Reviewer recognizes the challenge in recruiting young JRA patients less than 2 years of age for such a clinical trial.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

Refer to Appendix 10, 10.2 Line-By-Line Labeling Review for a line by line review.

10 APPENDIX

10.1 Review of Individual Study Reports

Protocol 134/135
Study Title
Protocol 134/135 was a Phase III, 12-week, parallel-group, double-blind, active comparator-controlled pivotal study to evaluate the efficacy and safety of rofecoxib for treatment of JRA in 2- to 17-year-old patients. This study was designed as a single study in concordance with the Pediatric WR.

Objectives

1. To examine the therapeutic effects of 2 doses of rofecoxib, taken as oral suspension, in 2- through 11-year-old JRA patients: 0.35 mg/kg/day, not to exceed 12.5 mg, and 0.7 mg/kg/day, not to exceed 25 mg.
2. To examine the therapeutic effects of 2 doses of rofecoxib, taken as tablets, in 12- through 17-year-old JRA patients: 12.5 and 25 mg once daily.
3. To demonstrate the safety and tolerability of rofecoxib in children with JRA.
4. To examine the safety and efficacy profile of naproxen for treatment of JRA, and compare with that of rofecoxib.
5. To examine treatment effects in patients with pauciarticular and polyarticular type JRA, respectively.

Study Design
Allocations were stratified by joint involvement (e.g., pauciarticular and polyarticular disease) and age group, to obtain approximate equal numbers of 2- to 11-year-olds and 12- to 17-year-olds. The study was monitored centrally to ensure that at least 20% of patients of the 2- to 11-year-old group were 2 to 5 years old.

The purpose of this study was to gain safety and efficacy experience with rofecoxib in polyarticular and pauciarticular JRA patients. For ethical reasons, the study did not include a placebo arm or a formal pre randomization flare. The magnitude of treatment effect was expected to be less than if a per-protocol worsening in signs and symptoms had been required prior to allocation. The active comparator, naproxen, was a nonselective NSAID (COX-1/COX-2 inhibitor) approved for and commonly used in pediatric arthritis patients. The inclusion of naproxen as an active comparator permitted the safety and efficacy of rofecoxib to be analyzed in the context of a currently approved therapy with a pediatric indication for relief of signs and symptoms of JRA. Safety and tolerability in the long-term treatment were assessed in a 12-month open-label extension study. Assessment of the durability of the treatment effect of rofecoxib was a secondary objective of the Extension study.

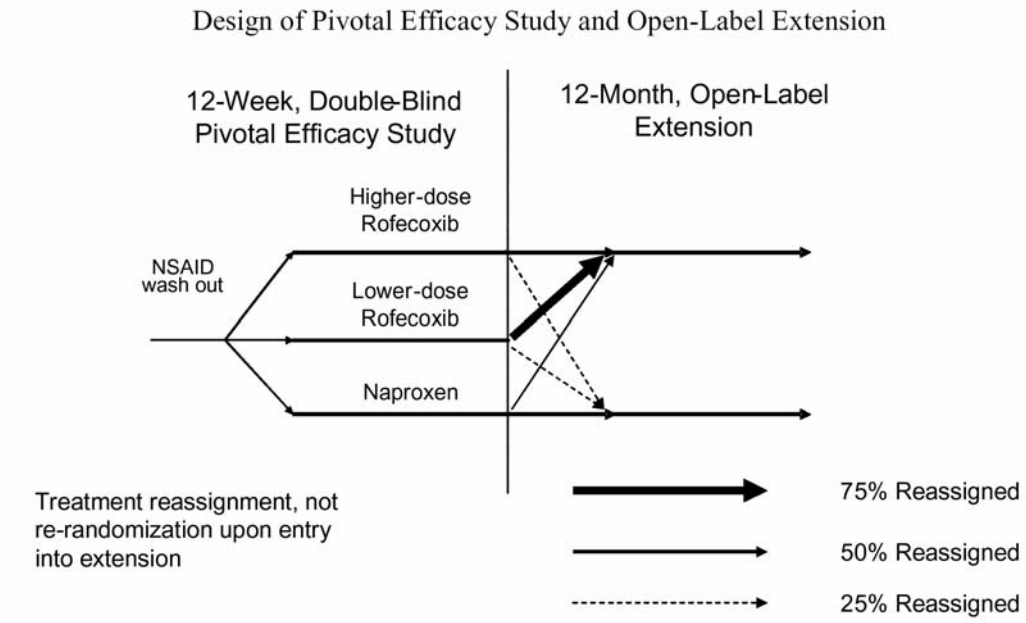
Study Medication/s
Ongoing stable DMARD therapies were permitted, but only if doses were anticipated to remain unchanged over the study course. Eligible patients underwent a brief washout of prior NSAID therapy and were assigned to 1 of 3 treatment groups, as noted if figure 1, in approximately equal proportions:

(1) Lower-dose rofecoxib; 0.3 mg/kg/day in
    2- to 11-year-olds (not to exceed 12.5 mg/day),
    12.5 mg daily in 12- to 17-year-olds;
(2) Higher-dose rofecoxib; 0.6 mg/kg/day in
    2- to 11-year-olds (not to exceed 25 mg/day),
    25 mg daily for 12- to 17-year-olds;
(3) Naproxen; targeted to 15 mg/kg/day.

Patients 2 to 11 years old received suspension formulations, and 12 to 17 years old received tablets. Acetaminophen was permitted as rescue medication for pain, but use was prohibited within 24 hours of scheduled clinic visits.

Extension Study of Protocol 134/135 assigns patients to one of two arms, higher dose rofecoxib versus naproxen. Safety and tolerability in the long-term treatment were assessed in this 12-month open-label extension study. Assessment of the durability of the treatment effect of rofecoxib was a secondary objective of the Extension study. Patients were reassigned upon entry into the extension study so that approximately two-thirds were in the higher-dose rofecoxib treatment group. See **Figure 2.**

Figure 2. Protocol 134/135, Design of Pivotal Efficacy Study and Open-Label Extension
(Figure from the sponsor's submission, section 2.7.3, figure 2.7.3:1)



Concomitant Medications

As described by the sponsor, in general, DMARDs and systemic corticosteroids must have been at stable doses for at least 6 and 4 weeks, respectively, prior to study entry. Tumor Necrosis Factor (TNF) sequestrant use must have been stable for at least 3 months. Otherwise, patients must have had a stable medical regimen for 2 weeks prior to pre-study screening. Patients must not have started new medications, stopped prior medications, or had a dose adjustment of a continuing medication during this period and prior to receiving Part I treatment. Patients are not to take NSAIDs, salicylates, or COX-2 specific inhibitors before study treatment, and until the day after discontinuation. Exception: low-dose aspirin, up to 100 mg daily, is allowed as anti-platelet therapy. Other prohibited medications are as below:

- Systemic corticosteroids at a dose >0.2 mg/kg/day of prednisone, not to exceed a total dose of 10 mg. (Intra-articular or periarticular corticosteroids are highly discouraged during the study course; the Merck monitor must be notified of such use immediately, including the dose, specific preparation, and site of administration. Only 1 intra-articular corticosteroid injection will be permitted per patient, during the study.)
- Alkylating agents

- Anti-convulsants
- Warfarin
- Rifampicin

Any patient on theophylline will have drug levels checked at each scheduled visit.

Study Visits

Follow-up clinical assessments were performed at 2, 4, 8, and 12 weeks on study therapy.

Table 40. Protocol 134/135 Study Visits

Weeks on Study Treatment	Prestudy	Allocation	2	4	8	12 or Discon-tinuation	Post-study
Clinic Visit I.D.:	1.0	2.0	3.0	4.0	5.0	6.0	7.0
Consent	X						
Patient's assessment of overall well being	X	X	X	X	X	X	
Patient's assessment of functional ability (CHAQ)	X	X	X	X	X	X	
Patient's assessment of pain	X	X	X	X	X	X	
Medical history/interim medical history	X	X	X	X	X	X	X
Temperature	X	X				X	
Vital signs and weight	X	X	X	X	X	X	X
Physical examination	X					X	
Active joint total‡		X					
Joint assessments	X	X	X	X	X	X	
Investigator's assessment of disease activity	X	X	X	X	X	X	
Hematology laboratories (CBC)	X	X	X	X	X	X	X
Chemistry laboratories	X	X	X	X	X	X	X
Serum β-hCG (menarchal girls)	X						
Urine β-hCG (menarchal girls)		X	X	X	X	X	X
Urinalysis†	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	
Dispense study medication		X	X	X	X		
Collect and count study medication			X	X	X	X	

† Sites to notify sponsor should urine collection not be feasible.
‡ It is only required that the investigator total the number of active joints at Visit 2.0.

Selection of Patients, Sample Size and Power Calculations

Approximately 110 pediatric patients, 2 years through 11years old and 110 pediatric patients, 12 years through 17 years old JRA patients will be included. Subgroups analyzed are shown in **Table 41**. The study will be monitored centrally to ensure that at least 20% of patients in the younger age group are 5 years old or younger. The sample size N=75 per dose group has at least 90% power to yield the 95% CI for the ratio of percent of patients improved greater than 0.5, if the true rates are equal for rofecoxib and naproxen and exceed 40%. This was computed using the log transformation of the ratio of 2 binomial rates and the normal approximation to the binomial distributions.

According to the sponsor, by using the log transformation of the ratio of 2 binomial rates and the normal approximation to the binomial distributions, the sample size N=100 per dose group had 99% power to yield the 95% CI for the ratio of JRA 30 response rate greater than 0.5, if the true rates are equal for rofecoxib and naproxen and exceed 40%.

Table 41. Protocol 134/135, Subgroups Defined by Criteria and Corresponding Variables
(This table is from the sponsor's submission, Table 11, section 5.7, page 60 of 2398.)

Prespecified Criteria:	Variables:
Protocol	• US (Protocol 134) • International (Protocol 135)
Joint involvement	• Pauci-articular • Poly-articular
Age group	• 2- to 11-year-olds • 12- to 17-year-olds
Gender	• Female • Male
Tanner Stage	• 1 • 2 • 3 • 4 • 5
Ethnic group	• Black • Caucasian • Hispanic • Multi-racial • Other[†]
Duration of Juvenile Rheumatoid Arthritis (parent/patient reported)	• < median years • ≥ median years
Erythrocyte Sedimentation Rate	• 0 to 20 (normal) • ≥20 (abnormal)
Baseline methotrexate user	• Yes • No
Baseline low-dose corticosteroid user[‡]	• Yes • No
Baseline disease-modifying anti-rheumatic drugs (DMARD) user [§]	• Yes • No
Prior naproxen user[‖]	• Yes • No

Inclusion Criteria

1. Patients were to be ≥ 2 and ≤ 17 years old.
2. Patient were to have a diagnosis of pauci (oligo) or poly-articular JRA, without active systemic symptoms for 3 months prior to randomization, based on specified diagnostic criteria for JRA developed by the American college of Rheumatology.
3. Patient was to have a diagnosis of JRA for at least 3 months.
4. At screening visit (Visit 1.0), parent/patient's assessment of overall well being (100-mm VAS) <90 mm and at allocation (Visit 2.0) was to be >10 mm.
5. Patient was to have at least 1 active joint at allocation (Visit 2.0).
6. Menarchal girls were to have negative serum ®-human Chorionic Gonadotropin (®-hCG) pregnancy test within 14 days prior to the treatment period. If sexually active, girls were required to have used an acceptable method of contraception, (e.g., oral contraceptives) from 2 weeks prior to treatment until 2 weeks after the study was completed.
7. Parent or guardian and patient were to have agreed to the patient's participation in the study program as indicated by parental permission and assent, as appropriate,

respectively. The patient was willing to comply with study procedures, and was to be able to keep scheduled clinic visits.
8. Patient was to be judged in otherwise good health on the basis of medical history, physical examination, and routine laboratory data.
9. Patient was to be neither grossly over- nor underweight for age, having been within the fifth to ninety-fifth percentile of weight for height.

Exclusion Criteria
1. Patient was to be < 2 years of age or would have turned 18 before completing the treatment period.
2. The patient was to be, in the opinion of the investigator, mentally incapacitated.
3. Patient was to be in a situation (e.g., unreliable foster care) or had a condition which, in the investigator's opinion, may have interfered with optimal participation in the study.
4. Patient will not to be pregnant or nursing, or may be a sexually active girl unwilling to use sanctioned birth control or remain abstinent during the study.
5. Patient has not resolved all symptoms and signs of an acute systemic infection at least 2 weeks prior to the pre-study visit.
6. Patient will not have a history of clinically significant disease of the gastrointestinal (e.g., active peptic ulceration or inflammatory bowel disease), cardiovascular, hepatic (Child-Pugh score ε7), neurologic, renal, genitourinary, or hematologic systems, or had chronic hypertension.
7. Patient will not have an estimated creatinine clearance of <30 mL/min.
8. Patient will not have had surgery, donated a unit of blood, or participated in another clinical trial, within 4 weeks of randomization.
9. Patient will not have hypersensitivity (e.g., angioedema and/or bronchoconstriction) to aspirin and/or NSAIDs.
10. Patient will not have a specific contraindication to a 12-week course of an NSAID such as naproxen.
11. Patient will not have a history of any illness that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering rofecoxib to the patient.
12. Parent/patient's assessment of overall well being (VAS [Visual Analog Scale]) was >90 mm at the screening visit (Visit 1.0) and <10 mm at allocation (Visit 2.0).
13. Patient had less than 1 active joint at allocation (Visit 2.0).
14. Patient had unconventional or extreme dietary habits.
15. Unstable use of a tumor necrosis factor (TNF) sequestrant within the 3 months prior to randomization.
16. Patient was not to have abused drugs or alcohol.
17. Patient's routine arthritis medication regimen was not to be unstable. Doses of gold, methotrexate, sulfasalazine, and anti-malarials must have been stable for at least 6 weeks before randomization and anticipated to remain stable for the duration of the study. Corticosteroid doses (maximum equivalent of 0.2 mg/kg/day prednisone, not to exceed 10 mg) must have been stable for at least 4 weeks before randomization and anticipated to remain stable for the duration of the study. Any other medications taken for JRA at the time of screening must have been stable for 4 weeks before randomization, and

except for NSAIDs, including salicylates and COX-2 inhibitors (which cannot be continued on study treatment), must have been anticipated to remain stable for the duration of the study.
18. Patient had received an intra-articular corticosteroid injection (e.g., triamcinolone acetonide) in the 4 weeks before randomization (3 months if preparation was triamcinolone hexacetonide).
19. Patient's other medical regimen had not been stable (i.e., medications had been started, stopped, or had adjustments in dosage) within 2 weeks prior to screening.
20. Patients were to use any of the following medications during the study.
- Salicylates, NSAIDs (including topical preparations in Part I), or non-study COX-2-specific inhibitors during the treatment period. (Exception: low-dose aspirin up to 100 mg daily was permitted as antiplatelet therapy.)
- Systemic corticosteroids at a dose >0.2 mg/kg/day of prednisone, not to exceed a total dose of 10 mg. (Intra-articular or periarticular corticosteroids were highly discouraged during the study course; the Merck monitor must have been notified of such use immediately, including the dose, specific preparation, and site of administration. Only 1 intra-articular corticosteroid injection was permitted per patient, during the study. Once injected, any joint was subsequently rendered "not evaluable" for purposes of joint counts.)
- Alkylating agents
- Anti-convulsants
- Warfarin
- Rifampicin

Other Exclusions
21. Significant laboratory abnormalities (as determined by Merck monitor or investigator) including transaminases >120% above the upper limit of normal.

Efficacy Variables
Primary Endpoints
The proportion of patients meeting the JRA Definition of Improvement ≥ 30% (JRA DOI 30) was selected as the primary endpoint based on regulatory guidance. The JRA DOI 30 was developed by a consensus process similar to the development of the ACR 20 (American College of Rheumatology 20) endpoint used in adults with RA. A clinically meaningful improvement using the JRA DOI 30 of at least 30% in any 3 of the 6 core variables, with no more than 1 of the remaining variables worsened by more than 30%. The core set of 6 variables for the JRA DOI 30 are:
1. Physician global assessment of overall disease activity (measured on a 100 mm visual analogue scale [VAS]);
2. Parent/patient's assessment of overall well-being (100-mm VAS);
3. Functional ability;
4. Number of joints with active arthritis (defined as the presence of swelling or limitation of motion with heat, pain, or tenderness);
5. Number of joints with limited range of motion; and
6. ESR.

Secondary Endpoints
The key secondary endpoint was the proportion of patients that demonstrated improvement from baseline in parent/patient's assessment of overall well being. This was an established JRA efficacy measurement tool and appeared to be a useful efficacy measure, based on exploratory efficacy data gathered during the clinical pharmacology studies. There is limited information about the performance of endpoints in JRA studies of NSAIDs versus DMARDs. The Sponsor retained it as the key secondary endpoint to preserve its relative priority in the analysis of study results.

Other Efficacy Endpoints
Other secondary endpoints in priority order included:

- Parent/patient's global assessment of pain (VAS)
- Proportion of patients discontinuing due to lack of efficacy

JRA 30 Core Set of Variables

- Parent/patient's assessment of overall well-being
- Investigator's global assessment of disease activity
- Patient's assessment of functional ability (CHAQ)
- Number of joints with active arthritis
- Number of joints with limited range of motion
- ESR

Note the following pertinent comments: Pain relief is one of the important benefits of NSAID therapy in JRA, yet it is not a component of the JRA DOI 30 definition of improvement.[1] The sponsor included this endpoint, independent of the JRA DOI 30, to enhance the understanding potential benefits of rofecoxib from this study. The parent or the patient, if deemed competent by the investigator, completed the assessments of overall well-being and pain. Functional ability was assessed using the Childhood Health Assessment Questionnaire (CHAQ), a validated, reliable, and sensitive instrument for measuring functional status in 1year to 19 year old children with JRA [2]

The primary measure of improvement for each endpoint will be time-weighted average change from baseline across all treatment visits (Visit 3.0 through Visit 6.0 and any unscheduled visits between 2.0 and 6.0). Visit 2.0 is considered baseline. In addition, mean change from baseline (± SE) by treatment group will be summarized at each observation week in single variable plots; for these plots only, missing values will be imputed via the last value carried forward technique. Data for core set components will be collected at Visit 1.0 to 6.0 (or discontinuation).

1. Giannini EH, Ruperto N, Ravelli A, et al. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997; 40:1202-9.

2. Singh G, Athreya BH, Fries JF, et al: Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 37: 1761, 1994.

Statistical Analysis Plan

A comprehensive Statistical Data Analysis Plan (DAP) was prepared prior to unblinding of the study data. All analyses were conducted in accordance with the Data Analysis Plan. A summary of the major statistical procedures follows. See Statistic Review by Atiar M. Rahman, PhD.

Approaches to Analyses
The approaches for the base study data analyses are noted in **Table 42.**

Table 42. Efficacy Endpoints and Their Statistical Analyses in the Pivotal Efficacy Study and the Extension to the Pivotal Efficacy Study
(Table 10 is from the sponsor's submission, Section 5.7, Table 10, page 59 of 2398.)

Endpoint	Statistical Method	Analysis Approaches
Primary		
Proportion of Patient Meeting the JRA 30 Criteria	Mantel-Haenszel method	MITT and PP
Key Secondary		
Proportion of Patient with Improvement from Baseline in Parent/Patient's Assessment of Overall Well-being	Mantel-Haenszel method	MITT
Other Secondary		
Patient's Global Assessment of Pain	ANCOVA	MITT
Discontinuation Due to Lack of Efficacy	Fisher's exact test	MITT
JRA 30 Core Set of Variables:		
Parent/Patient's Assessment of Overall Well-Being	ANCOVA	MITT
Investigator's Global Assessment of Disease Activity	ANCOVA	MITT
Functional Ability (CHAQ)	ANCOVA	MITT
Number of Joints With Active Arthritis	ANCOVA	MITT
Number of Joints With Limited Range of Motion	ANCOVA	MITT
Erythrocyte Sedimentation Rate	ANCOVA (log scale)	MITT

ANCOVA = Analysis of Covariance.
CHAQ = Child Health Assessment Questionnaire.
MITT = Modified Intention To Treat.
PP = Per Protocol.

Modified Intent-To-Treat Approach (MITT)
The Modified Intent-To-Treat (MITT) population was defined as all patients with a baseline visit and at least one on-treatment-period measurement. Patients were excluded from an endpoint analysis if baseline or all on-treatment study data for that particular endpoint were missing. In longitudinal plots over the 12-week study, the last-value-carried-forward (LVCF) method was used to impute missing data at particular time points; however, no data were imputed for the time-weighted average response computation.

Primary efficacy analyses were based on a modified intention-to-treat (MITT) approach (i.e., inclusion of all patients with a baseline and at least one on treatment-

period measurement). All measurements (except those from post study visits) were used, including data collected at discontinuation and unscheduled visits. Dropouts were included in the analysis based on responses obtained up to and including those at the time of discontinuation. Analyses were performed on the time-weighted average response of observed data only, while the last-value-carried-forward method was used only for longitudinal graphs. Since most of the endpoints were analyzed as the time weighted averages over the treatment period, no missing values were imputed (i.e., data points were not carried forward), except for the longitudinal graphs. The MITT approach was the primary and only analysis for safety endpoints. No exclusions were made from the safety analyses, nor were safety data imputed. Measurements of laboratory variables at post-study visit were not included, but adverse experiences, which occurred within 14 days of the last test therapy were included.

Per Protocol Approach

Patients were excluded from the per-protocol (PP) approach in the primary endpoint analyses for the base study data if all base study data were missing, if the patient violated the MITT criteria, or if the patient had a pre-specified significant protocol violation. See Section 10 for details of the analysis of PP approach. The analysis of the PP approach does not contribute to the efficacy findings and will therefore not be discussed further. Patients with any of the following were excluded from the PP analysis: Parent/patient assessment of overall well-being (VAS) > 90 mm at screening visit; and Parent/patient's assessment of overall well being (VAS) < 10 mm at allocation.

Table 43. Number of Patients Excluded from the Efficacy Analyses for the JRA DOI 30 and Each Component of the JRA DOI 30 Core Set in the 12-Week Study
(This Table is from the sponsor's Table 14, Section 6.4, page 70-71 of 2398)

Endpoint/Treatment	Randomized	Included in MITT (Excluded From MITT)†	Included in PP (Excluded from PP)‡
JRA 30 Responder Regardless of Completion Status			
Lower-Dose Rofecoxib	109	106 (3)	97 (9)
Higher-Dose Rofecoxib	100	99 (1)	90 (9)
Naproxen	101	98 (3)	87 (11)
JRA 30 Responder and Completer			
Lower-Dose Rofecoxib	109	106 (3)	101 (5)
Higher-Dose Rofecoxib	100	99 (1)	92 (7)
Naproxen	101	99 (2)	94 (5)
Each Component of the JRA 30 Core Set			
Parent/Patient Assessment of Overall Well-Being (0 to 100 VAS)			
Lower-Dose Rofecoxib	109	109 (0)	101 (8)
Higher-Dose Rofecoxib	100	100 (0)	91 (9)
Naproxen	101	100 (1)	89 (11)
Investigator Global Assessment of Disease Activity			
Lower-Dose Rofecoxib	109	109 (0)	101 (8)
Higher-Dose Rofecoxib	100	100 (0)	91 (9)
Naproxen	101	100 (1)	89 (11)
Functional Ability (CHAQ; 0 to 3 Likert)			
Lower-Dose Rofecoxib	109	109 (0)	101 (8)
Higher-Dose Rofecoxib	100	100 (0)	91 (9)
Naproxen	101	99 (2)	88 (11)
Number of Joints With Active Arthritis			
Lower-Dose Rofecoxib	109	109 (0)	101 (8)
Higher-Dose Rofecoxib	100	100 (0)	91 (9)
Naproxen	101	100 (1)	90 (10)

Endpoint/Treatment	Randomized	Included in MITT (Excluded From MITT)†	Included in PP (Excluded from PP)‡
Number of Joints With Limited Range of Motion			
Lower-Dose Rofecoxib	109	109 (0)	101 (8)
Higher-Dose Rofecoxib	100	100 (0)	91 (9)
Naproxen	101	100 (1)	90 (10)
Erythrocyte Sedimentation Rate			
Lower-Dose Rofecoxib	109	101 (8)	94 (7)
Higher-Dose Rofecoxib	100	99 (1)	90 (9)
Naproxen	101	95 (6)	85 (10)

† (Excluded from MITT) = (Randomized) - (Included in MITT).
‡ (Excluded from PP) = (Included in MITT) - (Included in PP).

Dropouts will be included in the primary analysis based on their responses obtained up to and including the time of discontinuation. If the number of major protocol violations in Part I is not negligible, then a secondary analysis with protocol violations removed will be carried out. All protocol violations will be identified, and a decision about the need for a per-protocol analysis will be made prior to the unblinding of the data. The list of major protocol violations will be documented prior to unblinding the data.

The 95% CI for ratio of percent of patients demonstrating improvement from baseline (rofecoxib versus naproxen) will lie entirely [redacted] (b) (4)

Differences between rofecoxib doses and naproxen in proportions of patients with adverse experiences or exceeding predefined limits of change in laboratory or vital sign variables will be assessed in the context of the magnitude of the proportions and differences observed and their clinical relevance.

1. Mean change from baseline (averaged over all times of observation) will be compared between the 2 doses of rofecoxib in the 2 year through 11 year old JRA patients, stratified by joint involvement (pauciarticular versus polyarticular course).
2. Mean change from baseline (averaged over all times of observation) will be compared between the 2 doses of rofecoxib in the 12 year through 17 year old JRA patients, stratified by joint involvement (pauciarticular versus polyarticular course).
3. The safety and tolerability of rofecoxib in children with JRA will be assessed as described.
4. The safety and efficacy profile of naproxen for treatment of JRA will be assessed and compared with that of rofecoxib.
5. The effects of treatment in patients with pauci-articular and poly-articular disease will be assessed by stratification by this factor and assessing treatment-by-joint status (pauci versus poly) interaction.

There will be no unblinded interim analysis.

Statistical Analyses Not Planned
The Division requested additional analyses be performed for the primary endpoint, the proportion of patients meeting the JRA DOI 30 criteria. The proportion of patients meeting the JRA DOI 30 was evaluated among patients who completed the 12-week base study as well as among patients who either completed the 12-week base study or discontinued due to lack of efficacy with patients who discontinued due to lack of efficacy counted as non responders.

Prior naproxen user status and prior NSAID user status, which were not prespecified as subgroup factors in the DAP, were examined in the subgroup analyses since those 2 subgroup factors are of clinical interest. For ethnic subgroup analyses, the prespecified groups in the DAP were Black, Caucasian, Hispanic, Multi-racial, and other (included Asian, Eurasian, European, Indian (subcontinent) and Polynesian races). Since there were too few Black, Hispanic, and Other patients in the study population, it was decided to combine the 3 groups with the Multi-racial group so that the subgroup levels were Caucasian and Non- Caucasian (included Black, Hispanic, Multi-racial and Other) in the ethnic subgroup analyses. See Section 10. Subgroup Analysis

Analysis of Safety
Safety was assessed by physical examinations, vital signs, weight, laboratory safety, and reporting of adverse experiences. See Integrated Review of Safety in this NDA review. The MITT approach was the primary and only analysis for safety endpoints. No exclusions were made from the safety analyses, nor were safety data imputed.

Protocol Amendments
The original protocol was amended 3 times:
1. The first protocol amendment, 134/135-01, was a result of confirmatory pharmacokinetic studies in 2- to 5-year-olds. The results of those studies showed that the 0.7-mg/kg dose yielded a steady-state AUC (0-24 hr) that was approximately 25% higher than the steady-state AUC(0-24 hr) of the historical adult population treated with rofecoxib 25 mg. Based on assumed dose proportionality of rofecoxib in this dosing range, a dose of 0.6 mg/kg was predicted to better approximate the steady state exposure (e.g., AUC(0-24 hr) of adults receiving the 25-mg tablet). Therefore, instead of the original doses of 0.35 mg/kg/day (lower dose rofecoxib group) and 0.7 mg/kg/day (higher-dose rofecoxib group), the protocol was amended such that suspension was dosed at 0.3 mg/kg/day (lower dose rofecoxib group) and 0.6 mg/kg/day (higher-dose rofecoxib group). Two patients, AN 169 and 151, were dosed at the original dose of 0.7 mg/kg. These patients were maintained on that dose throughout the study.

2. The second protocol amendment, 134/135-02, included the following changes: Inclusion and exclusion criteria were changed to reflect the requirement of at least 1 active joint for allocation; the study design and study flow chart were modified to reflect the deletion of safety labs at Visit 5. The wording of patient's assessment of overall well being in the study procedures was revised to more accurately reflect the case report forms. The original protocol indicated that the written prompt for the question read,

"Considering all the ways that arthritis affects you, mark an X through the line for your all well being over the past 48 hours." The worksheet questioned how the patient was affected by arthritis during the preceding week. The wording of the joint survey in the study procedures was revised to more accurately reflect the case report forms. The changes included: the number of finger PIP joints to be assessed was amended from 8, which appeared in the protocol, to 10, which appeared on the case report form; the term, "glenohumeral," in the protocol, appeared as "shoulder" on the case report forms, "subtalar joint (2)-except for swelling" did not appear in the protocol, but appeared on the case report form; and "sacroiliac (2)-for tenderness only," did not appear in the protocol, but appeared on the case report forms.

3. The third protocol amendment, 134/135-03, described the change in primary efficacy endpoint to the JRA DOI 30. Individual components of the JRA DOI 30 including the patient's assessment of overall well-being (100-mm VAS), previously the primary endpoint, were also to be analyzed. These changes were reflected in the Protocol Background and Rationale, Hypothesis, and Data Analysis.

52-Week EXTENSION, Protocol 134/135

Study Title
A 52-week, open-label, active-controlled extension to a 12-week, double-blind, double-dummy, active-controlled study in JRA patients ages ≥2 to ≤17 years.

Objectives
According to the sponsor, the purpose of this study was to obtain long-term safety and efficacy experience with rofecoxib in children with JRA. For ethical reasons, the trial did not include a placebo arm or a formal pre-randomization flare. Results should be interpreted in the context of an active-comparator controlled, self-selected, non-randomized group of patients, and the magnitude of treatment effect was expected to be less than if a per-protocol worsening in signs and symptoms had been required prior to allocation.

Study Design and Study Medications
The study design for Protocol 134/135 Open-label Extension Study is shown in **Figure 2.**

Patient Exposure
Patients 2 to 11 years old received rofecoxib or naproxen as a suspension formulation dosed by weight. The concentration of drug in the suspension was 5.0 mg/mL rofecoxib. Investigators were instructed to administer 0.12 mL of suspension per kg of the child's body weight at randomization once daily. The dose was not to exceed 5 mL (25 mg of rofecoxib). Patients assigned to naproxen received a 0.3-mL/kg twice-daily dose of a 25-mg/mL naproxen suspension.

Patients 12 to 17 years of age received rofecoxib 25 mg tablets once daily regardless of weight. Patients assigned to naproxen received 375 mg or 500 mg twice daily to approximate a 15 mg/kg daily dose. To achieve this, patients were

stratified by weight, ≤60 kg or >60 kg,

As determined by allocation in the base study, patients received 1 of 2 treatments in the open-label extension:
(1) rofecoxib; 0.6 mg/kg/day in patients allocated as 2 years to 11 years old (not to exceed 25 mg/day) [Note: at the investigator's discretion, patients were permitted to take 0.7 mg/kg/day (not to exceed 25 mg/day) if they had been randomized into the study prior to Amendment 134-12], or 25 mg daily for patients allocated as 12 year to 17 year olds; or
(2) naproxen; targeted to 15 mg/kg/day, with upward titration of naproxen permitted, if deemed appropriate by the investigator. See **Table 44.**

Table 44. Assignment, Treatment Groups, Extension Protocol 134/135, Open-Label
(Table is from the sponsor's submission, Section 5.1, Table 10, page 29 of 2044)

Base Study Treatment Group	**Extension Study Treatment Group**
Lower-dose rofecoxib	75% higher-dose rofecoxib
	25% naproxen
Higher-dose rofecoxib	75% higher-dose rofecoxib
	25% naproxen
Naproxen	50% higher-dose rofecoxib
	50% naproxen
Patients were assessed to 1 of 3 treatment groups at allocation into the base study and 1 of 2 groups in the open-label extension study.	

Twenty-five percent of patients allocated to low-dose rofecoxib in the base study were reassigned to naproxen treatment; the remaining 75% were reassigned to rofecoxib. Twenty-five percent of patients allocated to high-dose rofecoxib in the base study were reassigned to naproxen treatment; the remaining 75% continued on higher-dose rofecoxib. See **figure 2** and **Table 44.** Of patients allocated to naproxen in the base study, 50% were reassigned to higher-dose rofecoxib, and the remaining 50% continued on naproxen. Visit 8.0 took place at the same visit as Visit 6 in the base study.

Subsequent clinical assessments took place after 13 weeks in the open-label extension (Visit 9), 26 weeks in the extension (Visit 10), 39 weeks in the extension (Visit 11), and 52 weeks in the extension (Visit 12). In addition, 14-day post-study follow-up was required on all patients after discontinuation or completion of study drug.

Study Population and Sample Size
Sample size was determined by the number of patients who completed the base study and agreed to continue into the open-label extension. See **Table 45 and 46**. Three hundred ten patients were randomized into the base study. Two hundred eighty-five (91.9%) of patients completed the base study. Of these 285 patients, 227 (79.6%) entered the open-label extension.

Table 45. Patient Accounting in the Open-Label Extension 134/135
(Table is from the sponsor's submission, section 6.1, Table 12, page 57 of 2044)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg	Naproxen 15 mg/kg	Total
	n (%)	n (%)	n (%)
COMPLETED BASE STUDY			285
ENTERED:	160	67	227
COMPLETED:	134 (83.8)	47 (70.1)	181 (79.7)
DISCONTINUED:	26 (16.3)	20 (29.9)	46 (20.3)
Clinical adverse experience	4 (2.5)	8 (11.9)	12 (5.3)
Laboratory adverse experience	2 (1.3)	0 (0.0)	2 (0.9)
Lack of efficacy	3 (1.9)	1 (1.5)	4 (1.8)
Other reasons	17 (10.6)	11 (16.4)	28 (12.3)

Of the 227 randomized patients, 166 (73.1%) were girls and 61 (26.9%) were boys. The sample study was predominately White, 162 (71.4%) with the remaining 43 (18.9%) Multi-racial, 11 (4.8%) Hispanic American, 7 (3.1%) Black, 1(0.4%) Asian, 1 (0.4%) Eurasian, 1 (0.4%) European, and 1 (0.4%) Polynesian.

Patient ages ranged from 2 to 17 years. The mean age was 10.0 years, and the median age was 11.0 years. One hundred twenty-five (55.1%) of the patients were 11 years old or younger, while 102 (44.9%) were over 11 years old (See **Table 46**). Thirty-six (15.9%) of the patients who participated in the study were 2 to 4 years old, and 89 (39.2%) were 5 to 11 years old.

Table 46. Baseline Patient Characteristics by Treatment Group for Patients Who Entered the Open-Label Extension Protocol 134/135: Gender, Age, Race and Weight
(This Table is from the sponsor's submission, section 6.5, Table 14, p 64 of 2044.)

	Rofecoxib 0.6 mg/kg or Rofecoxib 25 mg (N=160)		Naproxen 15 mg/kg (N=67)		Total (N=227)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	117	(73.1)	49	(73.1)	166	(73.1)
Male	43	(26.9)	18	(26.9)	61	(26.9)
Age (Years)						
2 to 4 years†	23	(14.4)	12	(17.9)	36	(15.9)
5 to 11 years	67	(41.9)	23	(34.3)	89	(39.2)
12 to 17 years	70	(43.8)	32	(47.8)	102	(44.9)
Mean	10.0		10.1		10.0	
SD	4.13		4.45		4.24	
Median	11.0		11.0		11.0	
Range	2 to 17		2 to 17		2 to 17	
Race						
Asian	1	(0.6)	0	(0.0)	1	(0.4)
Black	6	(3.8)	1	(1.5)	7	(3.1)
Eurasian	0	(0.0)	1	(1.5)	1	(0.4)
European	0	(0.0)	1	(1.5)	1	(0.4)
Hispanic American	8	(5.0)	3	(4.5)	11	(4.8)
Multi-Racial	28	(17.5)	15	(22.4)	43	(18.9)
Polynesian	1	(0.6)	0	(0.0)	1	(0.4)
White	116	(72.5)	46	(68.7)	162	(71.4)
Weight of Patients 12 to 17 Years Old						
≤60 kg	59	(36.8%)	26	(38.8%)	85	(37.4%)
>60 kg	11	(6.9%)	6	(9.0%)	17	(7.5%)

† One patient, AN 96 (high-dose rofecoxib), who was 11 years old was incorrectly recorded in the database as 3 years old.

Inclusion Criteria

1. Patient completed the 12-week base study without major protocol violation and had no important clinical contraindication to continuing study treatment. See Appendix 1 for naproxen and rofecoxib product circulars.
2. Menarchal girls had negative beta-human Chorionic Gonadotropin (®-hCG) pregnancy tests, and if sexually active, used an acceptable method of contraception, (e.g., oral contraceptives) until 2 weeks after the study is completed.
3. Parent or guardian and patient agreed to the patient's participation in the extension-study program as indicated by informed consent. The patient was willing to comply with study procedures and was able to keep scheduled clinic visits.
4. Patient was judged to be in continuing good health, with the exception of underlying JRA, on the basis of medical history, physical examination, and routine laboratory data.

Exclusion Criteria

1. The patient had been inappropriately allocated in the base study.
2. The patient had a major protocol violation in the base study.
3. The patient had a significant clinical contraindication to continuing study drug
4. Patient was in a situation (e.g., unreliable foster care) or had a condition which, in the investigator's opinion, would interfere with optimal participation in the extension study.
5. Patient was pregnant, nursing, or sexually active and unwilling to use sanctioned birth control method or remain abstinent during the study.
6. The patient used any of the following medications during the study. Systemic salicylates, NSAIDs, or nonstudy COX-2-specific inhibitors during the treatment period. Exception: low-dose aspirin, up to 100 mg daily, was permitted as antiplatelet therapy, if clinically indicated. Systemic corticosteroids at a dose greater than 0.2 mg/kg/day of prednisone (not to have exceeded a total dose of 10 mg).
    - Alkylating agents.
    - Anti-convulsants.
    - Warfarin.
    - Rifampicin.

Efficacy Variables

Primary Efficacy Endpoint

The primary endpoint was the proportion of patients who met the JRA 30 criteria. The JRA 30 responder criteria are a core set of outcome variables for the assessment of children with JRA. Developed for assessment of impact of DMARD therapy on disease, improvement in patients with JRA according to these criteria were defined as at least 30% improvement from baseline in any 3 of the 6 variables in the core set, with no more than 1 of the remaining variables worsened by more than 30%. There are 6 variables included in the JRA DOI 30. See Protocol 134/135. In addition to assessment of disease activity, an assessment of the patient's pain was conducted, using the Patient's Global Assessment of Pain.

Secondary Efficacy Endpoints

The key secondary endpoint was the proportion of patients that demonstrated improvement from baseline in parent/patient's assessment of overall well being. Other secondary endpoints included:

- investigator's global assessment of disease activity
- patient's assessment of functional ability (CHAQ)
- number of joints with active arthritis
- number of joints with limited range of motion
- erythrocyte sedimentation rate
- parent/patient's global assessment of pain (VAS)
- proportion of patients discontinuing due to lack of efficacy

Statistical Analyses
The proportion of patients meeting the JRA30 criteria and completing the open-label extension was analyzed as a secondary analysis of this endpoint. The proportion of patients meeting the JRA 30 criteria and the proportion of patients demonstrating improvement from baseline in parent/patient's assessment of overall well-being were assessed by the Mantel-Haenszel estimate and resultant 95% CI for relative risk with protocol, joint involvement and age group as stratification factors.

No interim analysis was performed before the open-label extension data were fully cleaned and frozen; however, the study database was unblinded after the base study.

Compliance
The mean compliance rates during the open-label extension were 100.3% and 92.5% in the rofecoxib and naproxen treatment groups, respectively. The compliance rate was 98.0% across treatment groups.

Analysis of Safety
Safety was assessed by physical examinations, vital signs, weight, laboratory safety and reporting of adverse experiences.

Protocol Amendments
The original protocol was amended twice:

- The first protocol amendment was a result of confirmatory pharmacokinetic studies in 2 to 5 year olds. The results of those studies showed that the 0.7 mg/kg dose yielded a steady state area under the concentration-time curve AUC(0-24 hr) that was approximately 25% higher than the steady state AUC(0-24 hr) of the historical adult population treated with rofecoxib 25 mg. Based on assumed dose proportionality of rofecoxib in this dosing range, a dose of 0.6 mg/kg was predicted to better approximate the steady state exposure (e.g., AUC(0- 24 hr) of adults receiving the 25-mg tablet). Therefore, instead of the original dose 0.7 mg/kg/day (higher-dose rofecoxib group), the protocol was amended such that suspension was dosed at 0.6 mg/kg/day. This amendment was implemented prior to the entry of patients into the open-label extension.
- The second protocol amendment included the change of the primary efficacy endpoint to JRA DOI 30.

Schedule of Visits, Open-Label Extension, Protocol 134/135
See Table 47.

Table 47. Open-Label Extension Study Protocol 134/135, Schedule of Study Visits
(This Table is from the sponsor's submission, section 5.5.1, Table 5, page 36 of 2044.)

Weeks on Study Treatment	12	25	38	51	64 or Discon-tinuation	Post-study
Clinic Visit I.D.:	8.0	9.0	10.0	11.0	12.0	13.0
Consent	X					
Parent/Patient's assessment of overall well being	X†	X	X	X	X	
Parent/Patient's assessment of functional ability (CHAQ)	X†	X	X	X	X	
Patient's global assessment of pain	X†	X	X	X	X	
Medical history/interim medical history	X†	X	X	X	X	X
Temperature	X†	X			X	
Vital signs and weight	X†	X	X	X	X	X
Physical examination	X†				X	
Tanner stage assessment	X				X	
Joint assessments	X†	X	X		X‡	
Investigator's assessment of disease activity	X†	X	X	X	X	
Hematology laboratories (CBC)	X†	X	X	X	X	X
Chemistry laboratories	X†	X	X	X	X	X
Serum β-hCG (menarchal girls)	X					
Urine β-hCG (menarchal girls)	X†	X	X	X	X	
Urinalysis	X†	X	X	X	X	X
Erythrocyte Sedimentation Rate	X†	X	X	X	X	
Dispense study medication	X	X	X	X		
Collect and count study medication	X†	X	X	X	X	

† Conducted as Visit 6.0 procedures in base study.
‡ Conducted as only part of a discontinuation visit occurring at or before Visit 10.0.
β-hCG=Beta-Human Chorionic Gonadotropin.
CBC=Complete blood count.
CHAQ=Child Health Assessment Questionnaire.

Clinical Pharmacokinetic Studies
See Section 5, Clinical Pharmacology, for this Medical Reviewer's comments about the PK studies. The following PK study results are analyzed in the Clinical Pharmacology review by Lei K. Zhang, PhD and Jenny J. Zheng, PhD.

Protocol 105
Study Title
An Open-Label, Oral Dose Study to Evaluate the Steady-State Plasma Concentration Profile of Rofecoxib, Followed by a 12-Week, Double-Blind, Active-Controlled Extension in Late-Stage and Postpubertal Adolescents with JRA

Protocol 109
Study Title
An Open-Label, Oral Dose Study to Evaluate the Steady-State Plasma

Concentration Profile of Rofecoxib in JRA Patients, 2 Years to 11 Years Old

Protocol 110

Study Title

An Open-Label, Oral-Dose Study to Evaluate the Steady-State Plasma Concentration Profile of Rofecoxib in Juvenile Rheumatoid Arthritis Patients, Aged 2 Years to 5 Years

Protocol 228

Study Title

A Single-Period Multiple-Dose Study in RA Patients To Investigate The Steady-State Plasma Concentration Profile Of Rofecoxib

10.2Line-by-line Labeling Review

See separate attachment

References

See references listed within the sections of this review.

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

/s/

Carolyn L. Yancey
6/4/04 11:32:46 AM
MEDICAL OFFICER

review vioxx ped rheum supplements

James Witter
6/4/04 01:03:40 PM
MEDICAL OFFICER
Concur