CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

Trade Name: Vioxx

Generic Name: Rofecoxib

Sponsor: Merck & Co., Inc.

Approval Date: August 19, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Labeling	X
Summary Review	X
Officer/Employee List	
Office Director Memo	X
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-042/S-026
NDA 21-052/S-019

Merck & Co., Inc.
Attention: Michele R. Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
RY33-200
Rahway, NJ 07065-0900

Dear Dr. Flicker:

Please refer to your supplemental new drug applications dated December 05, 2003, received December 05, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vioxx™ (rofecoxib) Tablets, 12.5 mg, 25 mg, and Suspension 12.5 & 25 mg/5 mL.

We acknowledge receipt of your submissions dated July 16, and August 02, 2004.

Your submission of August 02, 2004 constituted a complete response to our June 04, 2004 action letter.

These supplemental new drug applications provide for the use of Vioxx™ tablet and suspension for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years and older and who weigh 10 kg (22 lbs) or more.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for these applications.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information **about this drug product (i.e., a "Dear Health Care Professional" letter),** we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Barbara Gould, Regulatory Project Manager, at (301) 827-2506.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Acting Director
Division of Anti-Inflammatory, Analgesic, &
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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/s/

Brian Harvey
8/19/04 10:51:11 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-042/S-026
NDA 21-052/S-019

Merck & Co., Inc.
Attention: Michele R. Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
RY33-200
Rahway, NJ 07065-0900

Dear Dr. Flicker:

Please refer to your supplemental new drug applications dated December 05, 2003, received December 05, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
21-042	S-026	Vioxx™ (rofecoxib tablets) Tablets 12.5 mg, 25 mg,
21-052	S-019	Vioxx™ (rofecoxib suspension) Suspension 12.5 mg/5 mL, 25 mg/5 mL

We acknowledge receipt of your submissions for NDA 21-042/S-026 dated January 07, February 17, April 22, 29, and 30, May 07, and 21, 2004.

We also acknowledge receipt of your submissions for NDA 21-052/S-019 dated January 07, April 22, and 29, and May 07, and 21, 2004.

These supplemental new drug applications provide for the use of Vioxx™ tablet and suspension for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years and older and who weigh 10 kg (22 lbs) or more.

We completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit revised draft labeling and patient package information.

The pediatric clinical trial section of the draft package insert requires further revision. The patient package insert must be reformatted, prioritizing risk communication (safety information) first. Refer to the MedGuide format as an example of prioritized risk communication.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the [redacted] y incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Barbara Gould, Regulatory Project Manager, at (301) 827-2506.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Acting Director
Division of Anti-Inflammatory, Analgesic, &
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Brian Harvey
6/4/04 05:06:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

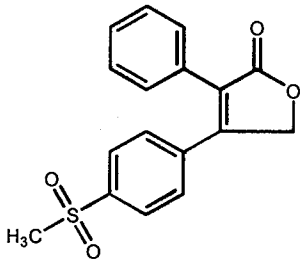
21-042 / S-026
21-052 / S-019

LABELING

VIOXX®
(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX* (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single **25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) ng/mL, respectively. Both C_{max}** and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was **4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively**, in healthy adults. The accumulation factor

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based on geometric means was 1.67. The AUC_{0-24hr} and C_{max} at steady state after multiple doses of **25 mg rofecoxib was 6934 (±2158) ng•hr/mL and 519** (±163) ng/mL, respectively, in adult RA patients (N=12, mean body weight 62 kg).

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX Tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/mL. The apparent volume of distribution at steady state (V_{dss}) is approximately 91 L following a 12.5-mg dose and 86 L following a 25-mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the cis-dihydro and trans-dihydro derivatives of rofecoxib, which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see *Drug Interactions*.)

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

The steady state pharmacokinetics of rofecoxib was evaluated in patients ≥ 2 years to ≤ 17 years of age who weigh more than 10 kg with pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA). The apparent clearance after oral administration of rofecoxib in patients ≥ 12 years to ≤ 17 years of age was similar to that of healthy adults and higher than that of adult RA patients. The apparent clearance after oral administration of rofecoxib in patients ≥ 2 years to ≤ 11 years of age was less than that of adults and increased with age. The apparent oral clearance of rofecoxib increases with body weight (and body surface area). (See Table 1.)

Table 1
Rofecoxib Apparent Oral Clearance (CL/F, mean ± SD) in JRA Patients* and Adults.

	JRA patients			Adults	
Group	2- to 5-year-old (N=21)	6- to 11-year-old (N=13)	12- to 17-year-old (N=11)	Healthy Age range: 20-48 (N=26)	RA Patients Age range: 31-64 (N=12)
Body Weight (kg)(mean ± SD)	17 ± 2	29 ± 6	57 ± 13	77 ± 13	62 ± 11
CL/F (mL/min)	37 ± 15	52 ± 13	87 ± 21	96 ± 30	65 ± 20

* Pauciarticular and Polyarticular Course JRA

A dose of 0.6 mg/kg to a maximum of 25 mg once daily in patients ≥ 2 years to ≤ 11 years of age and body weight 10 kg or above and a dose of 25 mg once daily in patients ≥ 12 years to ≤ 17 years of age would yield an AUC slightly higher than that of the 25-mg tablet once daily in healthy adults (AUC Geometric Mean Ratio, 1.12) and slightly lower than that in adult RA patients (AUC GMR, 0.77).

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A single-dose pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that mean rofecoxib plasma concentrations were higher (mean AUC: 55%; mean C_{max}: 53%) relative to healthy subjects. Since patients with hepatic insufficiency are prone to fluid retention and hemodynamic compromise, the maximum recommended chronic dose of VIOXX for patients with moderate hepatic insufficiency is 12.5 mg daily. (See PRECAUTIONS, *Hepatic Effects* and DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*.) Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended. (See WARNINGS, *Advanced Renal Disease*.)

Drug Interactions (Also see PRECAUTIONS, *Drug Interactions*.)

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with the recommended doses of rofecoxib have identified potentially significant interactions with rifampin, theophylline, and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Adults

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies); this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional arthritis medication during the last 6 months.

Rheumatoid Arthritis (RA)

VIOXX has demonstrated significant reduction of joint tenderness/pain and joint swelling compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of RA in two 12-week placebo- and active-controlled clinical trials that enrolled a total of approximately 2,000 patients. VIOXX was shown to be superior to placebo on all primary endpoints (number of tender joints, number of swollen joints, patient and physician global assessments of disease activity). In addition, VIOXX was shown to be superior to placebo using the American College of Rheumatology 20% (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures of RA. VIOXX 25 mg once daily and naproxen 500 mg twice daily showed generally similar effects in the treatment of RA. A 50-mg dose once daily of VIOXX was also studied; however, no additional efficacy was seen compared to the 25-mg dose.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Migraine with or without aura

The efficacy of VIOXX in the acute treatment of migraine headaches was demonstrated in two double-blind, placebo-controlled, outpatient trials. Doses of 25 and 50 mg were compared to placebo in the treatment of one migraine attack. A second dose of VIOXX was not allowed in either trial. In these controlled short-term studies, patients were predominantly female (88%) and Caucasian (84%), with a mean age of 40 years (range 18 to 78). Patients were instructed to treat a moderate to severe headache. Headache relief, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of relief was assessed for up to 24 hours postdose. Other medication, with the exception of NSAIDs (including COX-2 inhibitors) or combination medications that contained NSAIDs, was permitted from 2 hours after the dose of study medication. The frequency and time to use of additional medications were also recorded.

In both placebo-controlled trials, the percentage of patients achieving headache relief 2 hours after treatment was significantly greater among patients receiving VIOXX at all doses compared to those who received placebo (Table 2). There were no statistically significant differences between the 25- and the 50-mg dose groups in either trial.

Table 2
Percentage of Patients with Headache Relief (Mild or No Headache)
2 hours Following Treatment

Trial	VIOXX 25 mg	VIOXX 50 mg	Placebo
1	54%* (n=176)	57%* (n=187)	34% (n=175)
2	60%* (n=187)	62%* (n=188)	30% (n=187)

*p<0.0001 vs. placebo

Note that, in general, comparisons of results obtained in different clinical studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

The estimated probability of achieving initial headache relief within 2 hours following treatment is depicted in Figure 1.

Figure 1
Estimated Probability of Achieving Initial Headache Relief within 2 Hours

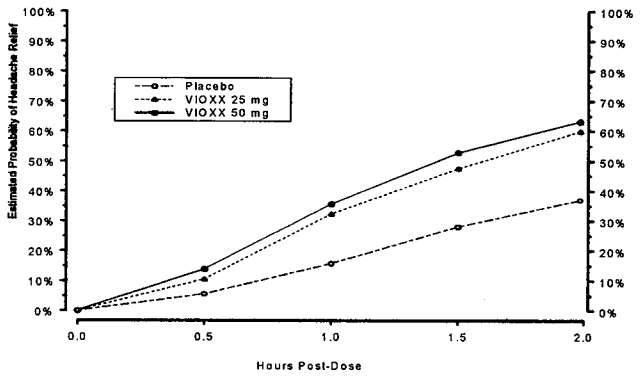
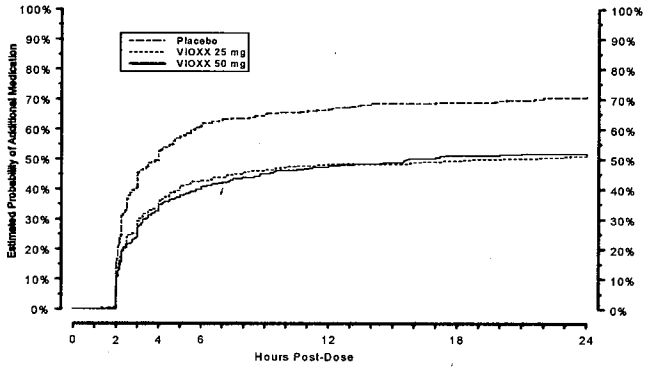


Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache relief (no or mild pain) following treatment with VIOXX or placebo. The plot is based on pooled data from the 2 placebo-controlled, outpatient trials in adults providing evidence of efficacy. Patients taking additional medication or not achieving headache relief prior to 2 hours were censored at 2 hours.

There was a decreased incidence of migraine-associated nausea, photophobia and phonophobia in VIOXX treated patients compared to placebo. The estimated probability of taking other medication for migraine over the 24 hours following initial dose of study treatment is summarized in Figure 2.

Figure 2
Estimated Probability of Patients Taking Additional Medication for Migraines over the 24 Hours Following the Initial Dose of Study Treatment



This Kaplan-Meier plot is based on pooled data obtained in 2 placebo-controlled outpatient trials. Patients not using additional medications were censored at 24 hours. The plot includes both patients who had headache relief at 2 hours and those who had no response to the initial dose. Additional medication was not allowed within 2 hours postdose.

VIOXX was effective regardless of presence of aura, gender, race, age, presence of menses or dysmenorrhea. Similarly, the concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives did not affect efficacy. VIOXX was also effective whether or not there was a history of prior response to NSAIDs.

Special Studies

The following special studies were conducted to evaluate the comparative safety of VIOXX.

VIOXX GI Clinical Outcomes Research (VIGOR Study)

Study Design

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX 50 mg once daily versus naproxen 500 mg twice daily was also studied. VIGOR was a randomized, double-blind study (median duration of 9 months) in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy (mean age 58 years). Patients were not permitted to use concomitant aspirin or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose aspirin for cardiovascular prophylaxis were to be excluded from the study. Fifty-six percent of patients used concomitant oral corticosteroids. The GI safety endpoints (confirmed by a blinded adjudication committee) included:

PUBs-symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding.

Complicated PUBs (a subset of PUBs)-upper GI perforation, obstruction or major upper GI bleeding.

Study Results

Gastrointestinal Safety in VIGOR

The VIGOR study showed a significant reduction in the risk of development of PUBs, including complicated PUBs in patients taking VIOXX compared to naproxen (see Table 3).

Table 3
VIGOR-Summary of Patients with Gastrointestinal Safety Events[1]
COMPARISON TO NAPROXEN

GI Safety Endpoints	VIOXX 50 mg daily (N=4047)[2] n[3] (Cumulative Rate[4])	Naproxen 1000 mg daily (N=4029)[2] n[3] (Cumulative Rate[4])	Relative Risk of VIOXX compared to naproxen[5]	95% CI[5]
PUBs	56 (1.80)	121 (3.87)	0.46*	(0.33, 0.64)
Complicated PUBs	16 (0.52)	37 (1.22)	0.43*	(0.24, 0.78)

[1]As confirmed by an independent committee blinded to treatment, [2]N=Patients randomized, [3]n=Patients with events, [4]Kaplan-Meier cumulative rate at end of study when at least 500 patients remained (approx. 10 1/2 months), [5]Based on Cox proportional hazard model

*p-value ≤0.005 for relative risk compared to naproxen

The risk reduction for PUBs and complicated PUBs for VIOXX compared to naproxen (approximately 50%) was maintained in patients with or without the following risk factors for developing a PUB (Kaplan-Meier cumulative rate of PUBs at approximately 10 1/2 months, VIOXX versus naproxen, respectively): with a prior PUB (5.12, 11.47); without a prior PUB (1.54, 3.27); age 65 or older (2.83, 6.49); or younger than 65 years of age (1.48, 3.01). A similar risk reduction for PUBs and complicated PUBs (approximately 50%) was also maintained in patients with or without *Helicobacter pylori* infection or concomitant corticosteroid use.

Other Safety Findings: Cardiovascular Safety

The VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily (see Table 4). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 5.) (See PRECAUTIONS, *Cardiovascular Effects*.) Adjudicated serious cardiovascular events (confirmed by a blinded adjudication committee) included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

Table 4
VIGOR-Summary of Patients with Serious Cardiovascular Thrombotic Adverse Events[1] Over Time
COMPARISON TO NAPROXEN

Treatment Group	Patients Randomized		4 Months[2]	8 Months[3]	10 ½ months[4]
VIOXX 50 mg	4047	Total number of events	17	29	45
		Cumulative Rate†	0.46%	0.82%	1.81%*
Naproxen 1000 mg	4029	Total number of events	9	15	19
		Cumulative Rate†	0.23%	0.43%	0.60%

[1]Confirmed by blinded adjudication committee, [2]Number of patients remaining after 4 months were 3405 and 3395 for VIOXX and naproxen respectively, [3]Number of patients remaining after 8 months were 2806 and 2798 for VIOXX and naproxen respectively, [4]Number of patients remaining were 531 and 514 for VIOXX and naproxen respectively.

†Kaplan-Meier cumulative rate.

* p-value <0.002 for the overall relative risk compared to naproxen by Cox proportional hazard model

Table 5
VIGOR- Serious Cardiovascular Thrombotic Adverse Events [1]

	VIOXX 50 mg N[2]=4047 n[3]	Naproxen 1000 mg N[2]=4029 n[3]
Any CV thrombotic event	45 *	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

[1]Confirmed by blinded adjudication committee, [2]N=Patients randomized, [3]n=Patients with events

* p-value <0.002 and ** p-value ≤0.006 for relative risk compared to naproxen by Cox proportional hazard model

For cardiovascular data from 2 long-term placebo-controlled studies, see PRECAUTIONS, *Cardiovascular Effects.*

Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis

The VIGOR study described above compared clinically relevant outcomes. Several studies summarized below have utilized scheduled endoscopic evaluations to assess the occurrence of asymptomatic ulcers in individual patients taking VIOXX or a comparative agent. The results of outcomes studies, such as VIGOR, are more clinically relevant than the results of endoscopy studies (see CLINICAL STUDIES, *Special Studies, VIGOR*).

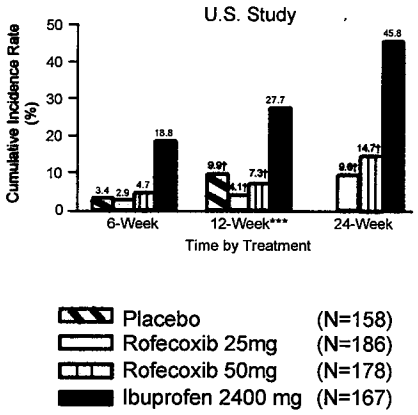
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. See Figures 3 and 4 for the results of these studies.

Figure 3

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3 mm (Intention-to-Treat)**

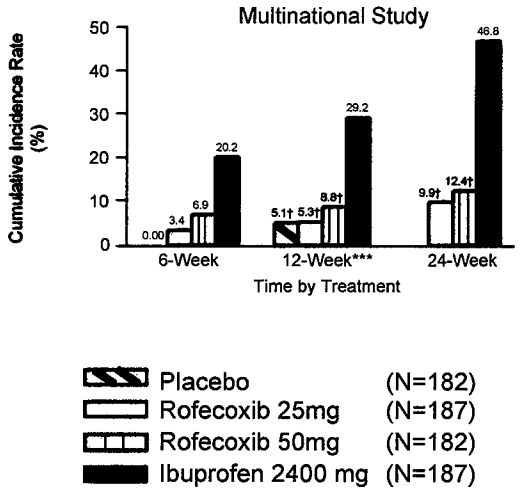


† $p < 0.001$ versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

Figure 4

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3 mm (Intention-to-Treat)**



† $p < 0.001$ versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

In a similarly designed 12-week endoscopy study in RA patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) or naproxen 1000 mg daily (common therapeutic dose), treatment with VIOXX was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with naproxen.

A similarly designed 12-week endoscopy study was conducted in OA patients treated with low-dose enteric coated aspirin 81 mg daily, low-dose enteric coated aspirin 81 mg plus VIOXX 25 mg daily, ibuprofen 2400 mg daily, or placebo. There was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose aspirin plus VIOXX 25 mg as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See PRECAUTIONS, *Drug Interactions, Aspirin.*)

Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation*).

Assessment of Fecal Occult Blood Loss in Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. (See PRECAUTIONS, *Cardiovascular Effects.*)

Pediatric Patients

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

In a 12-week, double-blind active-controlled, non-inferiority study, 310 patients, 2 years to 17 years of age with pauciarticular or polyarticular course JRA, received the following treatments: lower-dose VIOXX 0.3 mg/kg (to a maximum of 12.5 mg) once daily in patients ≥ 2 years to ≤ 11 years of age or VIOXX 12.5 mg once daily in patients ≥ 12 years to ≤ 17 years of age; higher-dose VIOXX 0.6 mg/kg (to a maximum of 25 mg) once daily in patients ≥ 2 years to ≤ 11 years of age or VIOXX 25 mg once daily in patients ≥ 12 years to ≤ 17 years of age; NSAID comparator targeted to an effective dose in patients ≥ 2 years to ≤ 17 years of age. The response rates were based upon the JRA Definition of Improvement ≥ 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates were 55% in both the VIOXX 0.6 mg/kg (to a maximum of 25 mg) and NSAID comparator treatment groups achieving the non-inferiority criterion. A single non-inferiority trial is not sufficient to support a conclusion of equivalence.

In a 52-week open-label extension to the 12-week study, 160 patients received VIOXX 0.6 mg/kg to a maximum of 25 mg once daily (patients ≥ 2 years to ≤ 11 years of age) or 25 mg once daily (patients ≥ 12 years to ≤ 17 years of age) and 67 patients ≥ 2 years to ≤ 17 years of age received NSAID comparator targeted to an effective dose. There were no unexpected safety findings.

INDICATIONS AND USAGE

VIOXX is indicated:
For relief of the signs and symptoms of osteoarthritis.
For relief of the signs and symptoms of rheumatoid arthritis in adults.
For relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older and who weigh 10 kg (22 lbs) or more.
For the management of acute pain in adults.
For the treatment of primary dysmenorrhea.
For the acute treatment of migraine attacks with or without aura in adults.

The safety and effectiveness of VIOXX have not been established for cluster headache, which is present in an older, predominantly male, population.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor

has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI outcomes research (VIGOR) study demonstrate that in patients treated with VIOXX, the risk of GI toxicity with VIOXX 50 mg once daily is significantly less than with naproxen 500 mg twice daily. (See CLINICAL STUDIES, *Special Studies, VIGOR.*)

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Previous studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving VIOXX. VIOXX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

Treatment with VIOXX is not recommended in patients with advanced renal disease. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Cardiovascular Effects

The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between the treatment groups. (See CLINICAL STUDIES, *Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.*) In a

placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, *Special Studies, Platelets*; PRECAUTIONS, *Drug Interactions, Aspirin.*) Prospective, long-term studies on concomitant administration of VIOXX and aspirin evaluating cardiovascular outcomes have not been conducted.

Fluid Retention, Edema, and Hypertension

Fluid retention, edema, and hypertension have been reported in some patients taking VIOXX. In clinical trials of VIOXX at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with VIOXX as compared to patients treated with naproxen 1000 mg daily. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of VIOXX at daily doses of 50 mg. (See ADVERSE REACTIONS.) VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, *Advanced Renal Disease*).

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including VIOXX. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. The maximum recommended chronic daily dose in patients with moderate hepatic insufficiency is 12.5 mg daily. Use of VIOXX is not recommended in patients with severe hepatic insufficiency (see CLINICAL PHARMACOLOGY, *Special Populations* and DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES, *Special Studies, Platelets*).

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with VIOXX and to reread it each time the prescription is renewed in case any information has changed.

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up. For additional gastrointestinal safety information see CLINICAL STUDIES, *Special Studies, VIGOR* and WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation*. Patients should be informed that VIOXX is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. For additional cardiovascular safety information see CLINICAL STUDIES, *Special Studies, VIGOR* and PRECAUTIONS, *Cardiovascular Effects*.

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, edema or chest pain to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. In a 12-week endoscopy study conducted in OA patients there was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose (81 mg) enteric coated aspirin plus VIOXX 25 mg daily, as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis*.)

At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TXB2 generation in clotting blood. Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL

STUDIES, *Special Studies, Platelets* and PRECAUTIONS, *Cardiovascular Effects.*) Prospective, long-term studies on concomitant administration of VIOXX and aspirin have not been conducted.

Cimetidine: Co-administration with high doses of cimetidine [800 mg twice daily] increased the C_{max} of rofecoxib by 21%, the $AUC_{0-120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In post-marketing experience there have been reports of increases in plasma lithium levels. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no effect on the plasma concentration of methotrexate as measured by AUC_{0-24hr} in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. At higher than recommended doses, VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by AUC_{0-24hr} in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Theophylline: VIOXX 12.5, 25, and 50 mg administered once daily for 7 days increased plasma theophylline concentrations ($AUC_{(0-\infty)}$) by 38 to 60% in healthy subjects administered a single 300-mg dose of theophylline. Adequate monitoring of theophylline plasma concentrations should be considered when therapy with VIOXX is initiated or changed in patients receiving theophylline.

These data suggest that rofecoxib may produce a modest inhibition of cytochrome P450 (CYP) 1A2. Therefore, there is a potential for an interaction with other drugs that are metabolized by CYP 1A2 (e.g., amitriptyline, tacrine, and zileuton).

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the AUC_{0-24}) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C.

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the **Pregnancy Registry at (800) 986-8999**.

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The use of VIOXX in patients with pauciarticular or polyarticular course JRA ≥ 2 years to ≤ 17 years of age was studied in pharmacokinetic studies and a 12-week, double-blind active-controlled study with a 52-week open-label extension. (See CLINICAL PHARMACOLOGY, *Pediatric;* CLINICAL STUDIES, *Pediatric Patients, Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA);* ADVERSE REACTIONS, *Pauciarticular and Polyarticular Course JRA.*)

Rofecoxib has not been studied in patients under the age of 2 years, with body weight less than 10 kg (22 lbs.), or in children with systemic type JRA.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older. This included 460 patients who were 75 years or older, and in one of these studies, 174 patients who were 80 years or older. No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. As with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients.

Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences occurring in ≥ 2.0% of Patients Treated with VIOXX in OA Clinical Trials				
	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heartbeat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder,

gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, hypersensitivity, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric: anxiety, depression, mental acuity decreased.

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection.

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, *hypertensive crisis*, myocardial infarction, *pulmonary edema*, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation*, duodenal ulcer, *esophageal ulcer*, *gastric perforation*, *gastric ulcer*, gastrointestinal bleeding, *hepatic failure*, *hepatitis*, intestinal obstruction, *jaundice*, pancreatitis.

Hemic and lymphatic: agranulocytosis, *aplastic anemia*, *leukopenia*, lymphoma, *pancytopenia*, *thrombocytopenia*.

Immune System: anaphylactic/anaphylactoid reaction, *angioedema*, *bronchospasm*, *hypersensitivity vasculitis*.

Metabolism and nutrition: hyponatremia.

Nervous System: aseptic meningitis, *epilepsy aggravated.*

Psychiatric: confusion, *hallucinations.*

Skin and Skin Appendages: photosensitivity reactions, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital System: acute renal failure, breast malignant neoplasm, *hyperkalemia*, *interstitial nephritis*, prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Rheumatoid Arthritis

Approximately 1,100 patients were treated with VIOXX in the Phase III rheumatoid arthritis efficacy studies. These studies included extensions of up to 1 year. The adverse experience profile was generally similar to that reported in the osteoarthritis studies. In studies of at least three months, the incidence of hypertension in RA patients receiving the 25 mg once daily dose of VIOXX was 10.0% and the incidence of hypertension in patients receiving naproxen 500 mg twice daily was 4.7%.

Analgesia, including primary dysmenorrhea

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

Migraine with or without aura

Approximately 750 patients were treated with a single dose of VIOXX 25 mg or 50 mg in two single-attack migraine studies. Approximately 460 patients in the 3-month extension phase of one study treated up to 8 (average 3) migraine attacks per month. In single attack studies, the following adverse events were more frequent in the VIOXX treatment groups (25 mg and 50 mg) compared to the placebo group, and occurred at an incidence of at least 2% of patients treated: dizziness, nausea, somnolence and dyspepsia. In the 3-month extension phase of one study, the following adverse events occurred at an incidence of at least 2% of patients treated in the VIOXX treatment groups (25 mg and 50 mg): dizziness, dry mouth, nausea, and vomiting.

Clinical Studies in OA and RA with VIOXX 50 mg (Twice the highest dose recommended for chronic use)

In OA and RA clinical trials which contained VIOXX 12.5 or 25 mg as well as VIOXX 50 mg, VIOXX 50 mg QD was associated with a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema, hypertension, serious* adverse experiences and discontinuation due to clinical adverse experiences compared to the recommended chronic doses of 12.5 and 25 mg (see DOSAGE AND ADMINISTRATION).

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

In a 12-week study, 209 JRA patients, ≥ 2 years to ≤ 17 years of age, were treated with rofecoxib; 109 and 100 patients were treated with lower-dose rofecoxib and higher-dose rofecoxib, respectively. In a 52-week open-label extension, 160 JRA patients, ≥ 2 years to ≤ 17 years of age, were treated with higher-dose rofecoxib for up to 15 months. No new adverse experiences were identified other than a single case of pseudoporphyria (a photo-induced blistering reaction), an adverse event that has been seen in patients with JRA treated with non-selective NSAIDs. In this 12-week study, the most common adverse experiences (at 0.6 mg/kg dose) were upper abdominal pain, nasopharyngitis, diarrhea, upper respiratory tract infection, abdominal pain, headache and rhinitis. Rash was also reported.

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

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*adverse experience that resulted in death, permanent or substantial disability, hospitalization, congenital anomaly, or cancer, was immediately life threatening, was due to an overdose, or was thought by the investigator to require intervention to prevent one of the above outcomes

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

Pediatric Patients	Daily Dose
≥ 2 years to ≤ 11 years of age and ≥ 10 to < 42 kg	0.6 mg/kg to a maximum of 25 mg*
≥ 2 years to ≤ 11 years of age and ≥ 42 kg	25 mg
≥ 12 years to ≤ 17 years of age	25 mg

*Oral suspension dosage form is recommended. To improve dosing accuracy in smaller weight children, the use of 12.5 mg/5 mL oral suspension (2.5 mg/mL) is recommended.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of VIOXX for more than 5 days in management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE REACTIONS, *Clinical Studies in OA and RA with VIOXX 50 mg*).

Acute Treatment of Migraine Attacks with or without aura

The recommended starting dose of VIOXX is 25 mg once daily. Some patients may receive additional benefit with 50 mg as compared to 25 mg. The maximum recommended daily dose is 50 mg. The safety of treating more than 5 migraine attacks in any given month has not been established. Chronic daily use of VIOXX for the acute treatment of migraine is not recommended.

Hepatic Insufficiency

Because of significant increases in both AUC and C_{max} in patients with moderate hepatic impairment (Child-Pugh score: 7-9), the maximum recommended chronic daily dose is 12.5 mg. (See CLINICAL PHARMACOLOGY, *Special Populations*). The efficacy of 12.5 mg in rheumatoid arthritis patients with moderate hepatic insufficiency has not been studied.

VIOXX Tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

HOW SUPPLIED

No. 3810 — Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3834 — Tablets VIOXX, 25 mg, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3835 — Tablets VIOXX, 50 mg, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-68 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-81 bottles of 4000.

No. 3784 — Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3784-64 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 — Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3785-64 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage

VIOXX Tablets:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued
Printed in USA

Patient Information about
VIOXX® (rofecoxib tablets and oral suspension)
VIOXX® (pronounced "VI-ox")
for Osteoarthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Pain and Migraine Attacks
Generic name: rofecoxib ("ro-fa-COX-ib")

You should read this information before you or your child start taking VIOXX*. Also, read the leaflet each time you refill a prescription, in case any information has changed. This leaflet provides only a summary of certain information about VIOXX. The doctor or pharmacist can give you an additional leaflet that is written for health professionals that contains more complete information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have questions about VIOXX ask your doctor or pharmacist.

What is VIOXX?

VIOXX is a prescription medicine called a COX-2 selective, nonsteroidal anti-inflammatory drug **(NSAID). (See section "What is VIOXX used for?")**

Who should not take VIOXX?

Do not take VIOXX if you or your child:

- have had an allergic reaction such as asthma attacks (wheezing), hives, or swelling of the throat and face to aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs). There are many NSAID medicines. Ask the doctor or pharmacist for a list of medicines that contain NSAIDs if you are not sure.
- are allergic to rofecoxib, the active ingredient of VIOXX, or to any other ingredients in VIOXX. See the end of this leaflet for a complete list of ingredients in VIOXX.

What are the possible side effects of VIOXX?

Serious but rare and potentially life-threatening side effects that have been reported in patients taking VIOXX include:

- Serious stomach problems, such as stomach and intestinal bleeding, can happen with or without warning symptoms. These problems, if serious, could lead to hospitalization or death. Although this does not happen often, you should watch for the signs and symptoms (for instance, stomach burning, vomiting blood, or if there is blood in the bowel movement or it is black and sticky like tar). Call your doctor right away if you or your child have any of these serious side effects.

- Serious allergic reactions include the symptoms and signs of swelling of the face, lips, tongue; trouble breathing such as chest tightness or shortness of breath; trouble swallowing; hives; wheezing; or shock (loss of blood pressure and consciousness). Get emergency help right away if you get any of these symptoms or signs. Serious skin reactions have also been reported.

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- Heart attacks and other serious cardiovascular events, such as blood clots in your body have been reported in patients taking VIOXX.

- Serious kidney problems can happen, including acute (sudden) kidney failure and worsening of chronic kidney failure.

- Severe liver problems, including hepatitis, jaundice and liver failure, can occur. Call your doctor if you or your child gets any of these symptoms of liver problems. These include: nausea; itching; pain in the right upper abdomen; yellow skin or eyes; or flu-like symptoms.

Your doctor may do blood tests and check you or your child for problems that may happen during treatment with VIOXX.

More common, but less serious side effects reported with VIOXX have included the following:

- Respiratory infections
- Headache
- Dizziness
- Diarrhea
- Nausea, vomiting and upset stomach
- Heartburn
- Stomach pain
- Swelling of the legs and/or feet
- High blood pressure
- Back pain
- Tiredness
- Urinary tract infection.

In addition, the following side effects have been reported: anxiety, blurred vision, colitis, confusion, constipation, decreased levels of sodium in the blood, depression, fluid in the lungs, hair loss, hallucinations, increased levels of potassium in the blood, insomnia, low blood cell counts, menstrual disorder, palpitations, pancreatitis, ringing in the ears, severe increase in blood pressure, skin reactions caused by sunlight, tingling sensation, unusual headache with stiff neck (aseptic meningitis), vertigo, worsening of epilepsy.

These are not all the side effects reported with VIOXX. Do not use this leaflet alone for information about side effects. Your doctor or pharmacist can talk to you about other side effects. Any time you or your child have a medical problem you think may be related to VIOXX, talk to your doctor.

What is VIOXX used for?

VIOXX is used in adults for:

- relief of the pain and inflammation (swelling and soreness) of osteoarthritis (arthritis from wear and tear on your bones and your joints)

- relief of the pain and inflammation of rheumatoid arthritis in adults (arthritis caused by a condition where your immune system attacks your joints)
- management of short-term pain
- treatment of menstrual pain (pain **during women's monthly periods)**
- treatment of migraine headache attacks with or without aura.

VIOXX is used in children and adolescents, of at least 2 years of age and who weigh at least 10 kg (22 lbs.) to help relieve:

- the signs and symptoms of pauciarticular or polyarticular Juvenile Rheumatoid Arthritis (JRA). VIOXX has not been studied in children with systemic type JRA.

VIOXX has not been studied in children less than 2 years old or with body weight less than 10 kg (22 lbs.).

What should I tell the doctor before and during treatment with VIOXX?

Tell your doctor about all your or yo**ur child's medical conditions includ**ing if you or your child have or have had:

- an allergic reaction to aspirin or other NSAIDs
- asthma (a small number of patients with asthma have reactions to aspirin or other NSAIDs)
- stomach problems such as ulcers or bleeding
- kidney disease
- liver disease
- angina (for instance, chest, arm, or jaw pain), a heart attack, or a blocked artery in the heart
- heart failure
- high blood pressure

Tell your doctor if you or your child are:

- pregnant or plan to become pregnant. VIOXX may harm your unborn baby if you take it in late pregnancy. If you take VIOXX while you are pregnant, ask your doctor how you can be on the VIOXX Pregnancy Registry.
- breast-feeding or plan to breast-feed. It is not known if VIOXX passes into your milk and if it can harm your baby. You should discuss with your doctor whether or not to take VIOXX if you are breast-feeding.

Tell your doctor about:

- any other medical problems or allergies you or your child have now or have had.
- all the medicines you or your child take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Tell your doctor right away if you or your child develop:

- serious stomach problems such as ulcer or bleeding symptoms (for instance, stomach burning, vomiting blood, or if there is blood in the bowel movement or it is black and sticky like tar.
- unexplained weight gain or swelling of the legs, feet, and/or hands.

- skin rash or allergic reactions. If you or your child have a severe allergic reaction, get medical help right away.

Can VIOXX be taken with other medicines?

Tell your doctor about all of the other medicines you or your child are taking or plan to take while you or your child are on VIOXX, even other medicines that you can get without a prescription, including vitamins and herbal supplements. VIOXX and certain other medicines can affect each other causing serious side effects. Keep a list of the medicines you or your child take. Show the list to your doctors and pharmacists each time you get a new medicine. They will tell you if it is safe to take VIOXX with other medicines. Especially tell your doctor if you or your child are taking:

- or have taken warfarin (Coumadin®) or any other similar blood thinner within the past 10 days
- theophylline (a medicine used to treat asthma)
- rifampin (an antibiotic)
- ACE inhibitors (medicines used for high blood pressure and heart failure)
- lithium (a medicine used to treat a certain type of depression).

VIOXX cannot take the place of aspirin for prevention of heart attack or stroke. If you or your child take both aspirin and VIOXX, there may be a higher chance of serious stomach problems than if VIOXX is taken alone. If you or your child are taking aspirin for prevention of heart attack or stroke, you or your child should not stop taking aspirin without talking to your doctor.

How should VIOXX be taken?

- Take VIOXX exactly as prescribed by the doctor. The dose will depend on the condition being treated and other medical problems you or your child may have. Do not change the dose of VIOXX or take extra doses unless the doctor has told you to.
- VIOXX may be taken with or without food.
- If you or your child miss a dose of VIOXX by a few hours, take it as soon as you remember. If it is close to the next dose, do NOT take the missed dose.
- If you or your child take too much VIOXX, call the doctor, pharmacist, or poison control center right away.

How should I store VIOXX?

- Store VIOXX at room temperature, 59° to 86°F (15° to 30°C).
- Safely throw away VIOXX that is out of date or no longer needed.
- Keep VIOXX and all medicines out of the reach of children.

What else should I know about VIOXX?

This leaflet provides a summary of certain information about VIOXX. If you have any questions or concerns about VIOXX talk to your health professional. Your doctor or pharmacist can give you an additional leaflet that is written for health professionals. This leaflet is also available at www.vioxx.com.

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use VIOXX for a condition for which it was not prescribed. Do not give VIOXX to other people even if they have the same symptoms you have. It may harm them.

What are the ingredients in VIOXX?

Active Ingredient: rofecoxib

Inactive Ingredients:

Oral suspension: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, sodium methylparaben, sodium propylparaben.

Tablets: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

Rx Only

Issued

MERCK & CO., Inc.
Whitehouse Station, NJ 08889, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

SUMMARY REVIEW

Clinical Team Leader's Memorandum:

Reviewer: James Witter MD, PhD (HFD-550)

Date: June 3, 2004

NDA: 21-042/S-026 and NDA 21-052/S-019

Sponsor: Merck Research Laboratories
Vioxx® (rofecoxib) tablets-12.5, 25 mg and suspension-12.5 mg/5 mL and 25 mg/5 mL

Summary:
NDA 21-042/ S-026 (tablets) and NDA 21-052/S-019 (suspension) is a pediatric efficacy supplement for the treatment of the signs and symptoms of pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years to 17 years of age. It was submitted December 5, 2003 in response to a pediatric Written Request (WR) issued by HFD-550 on May 7, 2001. The submission consisted of four PK studies (protocol 105, 109, 110 and 228) along with one 12-week, double-blind, active control, phase 3 clinical efficacy and safety study which was followed by a 52-week, open-label extension (see below, protocol 134/135).

PK studies
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.

Clinical Efficacy and Safety
Protocol 134/135 was a multi-center study that involved sites in Australia, Europe, Mexico, Israel, South America and United States. These protocols were identical and were assigned different numbers to differentiate the U.S. site (protocol 134) from the other multi-national sites (protocol 135). These studies consisted of a 12-week, double-blind, double-dummy, active-controlled study in 2 to 17 year old pauciarticular and polyarticular JRA patients. In this portion of the study, both a low-dose (0.3 mg/kg/d to a maximum of 12.5 mg/d) and high-dose (0.6 mg/kg/d to a maximum of 25 mg/d) rofecoxib suspension was compared to the active control (naproxen, 7.5 mg/kg BID). For children whose weight was greater than 40 kg, the corresponding rofecoxib tablet (12.5 or 25 mg) was employed rather than the suspension. Patients were then allowed to enter

the 52-week extension study which included only the higher-dose rofecoxib suspension or tablet compared to naproxen. The extension was intended to address the durability of the efficacy response and to continue to study safety. A total of 209 JRA patients were enrolled and exposed to rofecoxib (109 patients to lower dose, 100 patients to higher dose) during the 12-week portion of the study while 160 patients were enrolled into the extension portion of the study and exposed to high-dose rofecoxib.

Efficacy was assessed in this trial using the JRA-DOI (definition of improvement) ≥ 30% which is a valid metric in this JRA population (*Giannini, et.al. Arth. Rheum. 1997; 40: 1202-1209*). This study was designed as a non-inferiority trial with the lower margin of the point estimate of the 95% confidence interval pre-specified at ≥ 0.5. This margin was noted to be unacceptable to HFD-550 in the WR letter in that it was too low. Consequently, the lower margin for the 95% confidence interval of the point estimate of ≥ 0.75 was employed for the determination of efficacy for these two pediatric NDA supplements.

For the primary endpoint of JRA DOI 30, the point estimates and 95% CI for comparison to naproxen were as follows in a modified ITT during the 12-week portion of the study:

- **higher dose** (0.6 mg/kg rofecoxib)
  - regardless of completion status **(0.98: 0.76-1.26)**
  - completers **(1.00: 0.78-1.29)**
- lower dose (0.3 mg/kg rofecoxib)
  - regardless of completion status (0.81: 0.61-1.07)
  - completers (0.81: 0.61-1.09)

Therefore, since the lower limit of the point estimate was less than 0.75 in the lower-dose rofecoxib group, this dose was considered inferior to naproxen.

The proportion of patients who achieved the JRA DOI 30 criterion in the modified ITT population regardless of completion status, over the 12-week study was **46.2%, 54.5% and 55.1%** for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. At the end of the 52-week extension, the JRA DOI 30 (regardless of completion status) was 66.7% (rofecoxib) and 60.3% (naproxen); for completers the rates were 57.9% (rofecoxib) and 42.4% (naproxen) supporting the conclusion that the higher-dose rofecoxib offer long-term efficacy.

The safety of rofecoxib was established from this combined protocol. No deaths occurred and the adverse event profile obtained with rofecoxib did not reveal any new or unexpected findings with regards to short-or long-term safety other than the adverse event of pseudoporphyria in one child treated with higher-dose rofecoxib in the extension study.

Regulatory Action:
As noted above, the sponsor is interested in the INDICATION for treatment of JRA. Proposed revisions to the VIOXX labeling include additions to the **CLINICAL PHARMACOLOGY (Pediatric), Special Studies (Pediatric Patients), INDICATIONS and USAGE, Precautions (Pediatric Use),** and the **Adverse Reactions-(Pauciarticular and Polyarticular Course JRA)** section.
Following several teleconferences with the sponsor (including participation by DDMAC), the proposed changes to the label are not acceptable. In particular, use of the name of the active comparator (i.e. naproxen) is unacceptable as it has implications for implied (but unsubstantiated) promotional claims. In addition, the Patient Package Insert language is unacceptable since it is not following the proposed MedGuide format. Therefore, the action for the sponsor will be **APPROVABLE** pending agreement on the proposed labeling.

Appendix

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

/s/

James Witter
6/4/04 01:35:07 PM
MEDICAL OFFICER
Team Leader Memorandum

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301) 827-2040

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: August 5, 2004

DRUG: Vioxx (rofecoxib)

NDA: 21-042 (SE5-026)
21-052 (SE5-019)

SPONSOR: Merck & Co., Inc.

INDICATION: The treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis in patients 2 years and older and who weigh 10 kg or more

Merck & Co., Inc. submitted efficacy supplements for Vioxx™ (rofecoxib) for the indication of the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) to NDAs 21-042/S-026 (Tablets 12.5 mg and 25 mg) and 21-052/S-019 (Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL) on December 5, 2003. An Approvable action was taken on June 4, 2004. Although agreement was reached that the study submitted in support of efficacy demonstrated noninferiority to the comparator, agreement was not reached on the language to be added to the package insert describing the pediatric clinical trial. Agreement was also not reached on the Division's proposal to update the language and the organization of the patient package insert. As this was a pediatric efficacy supplement, upon taking an approvable action, the package was to go before the Pediatric Advisory Committee. However, as there was no disagreement over the scientific basis for a finding of noninferiority, and in consultation with the pediatric team, it was decided that if agreement on the language for the package insert and patient package insert could be reached with only a small amount of additional negotiation, it would not be necessary to go before the advisory committee.

The sponsor submitted a package insert and patient package insert on July 19, 2004. Following a discussion by telephone with the sponsor on July 29, 2004, agreement was reached and the final, agreed upon package insert and patient package insert were submitted on July 30, 2004. In particular, the description of the clinical trial in the package insert refers

to an NSAID comparator rather than naming naproxen and includes the proviso that a single non-inferiority trial is not sufficient to support a conclusion of equivalence. The patient package insert, while not in Med Guide format, has been reorganized to emphasize important risk information.

Action recommended by the Division: Approval

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V, CDER, FDA

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: June 4, 2004

DRUG: Vioxx (rofecoxib)

NDA: 21-042 (SE5-026)
21-052 (SE5-019)

SPONSOR: Merck & Co., Inc.

INDICATION: The treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis in patients 2 years and older and who weigh over 10 kg

Merck & Co., Inc. has submitted efficacy supplements for Vioxx (rofecoxib) for the indication of the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) to NDAs 21-042 (Tablets 12.5 mg and 25 mg) and 21-052 (Oral Suspension 12.5 mg/mL and 25 mg/mL). One 12-week double-blind, active-control efficacy study with a 52 week open-label extension and four pharmacokinetic studies, including one adult PK study to provide comparative data, have been submitted to support this indication and to fulfill the requirements of the Pediatric Written Request (PWR) issued December 6, 2001. A clinical review has been completed by Carolyn Yancey, M.D. Review of the clinical pharmacology and biopharmaceutics data was completed by Lei Zhang, Ph.D. and Jenny J. Zheng, Ph.D. A statistical review and evaluation was completed by M. Atiar Rahman, Ph.D. No new CMC nor nonclinical pharmacology data was submitted with this application. The studies submitted were considered adequate to fulfill the requirements of the PWR.

Rofecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug which has been approved for relief of the signs and symptoms of osteoarthritis, the relief of the signs and symptoms of rheumatoid arthritis in adults, the management of acute pain in adults, the treatment of primary dysmenorrhea, and most recently, for the acute treatment of migraine attacks with or without aura in adults. The most common adverse events reported in adults taking rofecoxib include abdominal pain, nausea, and heartburn, as well as upper respiratory infection, headache, and back pain. An additional concern is a risk of cardiovascular thrombosis identified during a gastrointestinal safety trial in adults with rheumatoid arthritis.

JRA can present in any of three predominant forms, systemic, polyarticular, and pauciarticular. Patients enrolled in the one study submitted in support of efficacy had predominantly polyarticular and pauciarticular JRA. The treatment of JRA centers on the use of disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, to slow the progression of the diseases, and nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of joint inflammation and pain. It is considered inappropriate to require patients with JRA to go without NSAID therapy, even with use of a DMARD. As a result, an active-control, non-inferiority design was accepted to support a finding of efficacy of rofecoxib for this indication.

Efficacy

Study 134/135 was a multi-center, 12-week, double-blind, active-control, noninferiority study comparing lower-dose rofecoxib (0.3 mg/kg/day up to 12.5 mg), higher-dose rofecoxib (0.6 mg/kg/day up to 25 mg), and naproxen 15 mg/kg/day in patients with pauciarticular and polyarticular JRA, stratified by form of JRA and age. Patients ages 2 through 11 were dosed with rofecoxib based on weight using the suspension formulation. Patients ages 12 through 17 were dosed at the 12.5 mg/day and 25 mg/day doses, using the tablet formulation, for the lower and higher-dose rofecoxib groups, respectively. Patients were washed out from prior NSAID therapy for 3 days, but were permitted to continue stable prior DMARD therapy. Acetaminophen was the prespecified rescue medication, but not permitted within 24 hours of an assessment. Subjects were eligible to enter a 52-week open-label extension on either higher-dose rofecoxib or naproxen.

The primary outcome measure was the JRA Definition of Improvement (DOI) 30, a composite score requiring at least 30% improvement in any three of the six core measures, provided there was no more than one of the variables worsening by >30%. These six measures are physician's global assessment of disease severity (10 cm VAS), patient's or parent's global assessment of overall well-being (10cm VAS), physical

function, as measured by Child Health Assessment Questionnaire Disability Index, number of joints with active arthritis, as defined by the American College of Rheumatology (ACR) criteria (a joint with swelling not due to deformity or a joint with limited range of motion plus pain and/or tenderness), number of joints with limited range of motion plus pain and/or tenderness, and erythrocyte sedimentation rate (ESR).

All of the 310 randomized patients received at least one dose of study medication. Two hundred eighty five patients completed the 12-week double-blind period. Discontinuations due to lack of efficacy were few, three patients from the lower-dose rofecoxib group, and four from both the higher-dose rofecoxib and naproxen groups. There were also few discontinuations due to adverse events (AEs), three from the lower-dose rofecoxib group and two from the naproxen group. The JRA DOI 30 responder rates were 46%, 55%, and 55% from the lower-dose rofecoxib, higher-dose rofecoxib, and naproxen groups, respectively. The 95% confidence interval (CI) for comparison of the lower-dose rofecoxib group and naproxen was 0.61 to 1.07. The 95% confidence interval for comparison of the higher-dose rofecoxib group and naproxen was 0.76 to 1.26. The margin for noninferiority for the lower bound of the CI set by the Sponsor was 0.50, but was considered too broad by the Division. For this analysis, the Division set the lower bound for noninferiority at 0.75 and by this criterion, the higher-dose rofecoxib, but not the lower-dose rofecoxib, was considered non-inferior to naproxen.

The individual components of the JRA DOI 30 were evaluated as secondary endpoints. Parent/patient assessment of overall well-being, physician global assessment of disease activity, CHAQDI, and ESR were similar across treatment groups. The number joints with active arthritis and number of joints with limited range of motion plus pain and/or tenderness trended better in the naproxen group, but the difference did not reach statistical significance.

The efficacy results for subgroups of patients ages 2 to 11 and 12 to 17 were examined and were qualitatively similar to the overall group of ages 2 to 17. The small number of patients overall preclude confident quantitative comparisons across subgroups.

Patients who elected to continue in the 52-week open-label extension received either higher-dose rofecoxib or naproxen based upon allocations made at the time of the initial randomization for the 12-week study. Although the efficacy endpoints from the 12-week study were measured, as the study was open-label, no conclusions about efficacy during the 52-week period can be made. The overall efficacy appeared durable during this time period.

Safety

Study 134/135 was the primary source for safety data with additional information obtained from the pharmacokinetic studies. A total of 357 patients were studied, 297 of whom received rofecoxib, 183 were 2 to 11 years of age and 114 were 12 to 17 years of age. The Sponsor did not provide any overall integrated accounting of AEs.

There were no deaths during any of the clinical trials submitted to the supplements under review. There were 21 serious adverse events (SAEs) according to the Sponsor. Dr. Yancey's review of the safety data yielded one additional SAE during the 12-week double-blind period of Study 134/135. This patient experienced worsening of JRA requiring hospitalization. Of the remaining 4 SAEs during the 12-week double-blind study, one patient was in the lower-dose rofecoxib group, one patient was in the naproxen group, and two patients were in the higher-dose rofecoxib group. All of these SAEs were worsening of JRA requiring hospitalization with additional symptoms including uveitis in one patient and gastroenteritis, fever, lymphadenopathy and anemia in one patient. There does not appear to be a causal relationship between these events and study drug.

During the 52-week extension, 10 patients in the rofecoxib group and seven in the naproxen group experienced SAEs. In the rofecoxib group, the SAEs were: two cases of worsening uveitis (including one patient with head trauma as well), and one case each of pneumonia, acute bronchitis, acute appendicitis, angina tonsillaris, hepatitis A, head injury sustained in an accident, accidental overdose of one additional dose of study drug, and *helicobacter pylori* infection with chronic gastritis. In the naproxen group, the SAEs were one case each of GI infection requiring IV hydration, varicella with mouth ulcers, gastroenteritis, inpatient reevaluation of JRA, abdominal pain with emotional distress, abdominal pain, and a patient with convulsions with sepsis, bone marrow depression and worsening JRA. There is no apparent relationship between the SAEs, other than abdominal pain, and study drug.

The adverse events resulting in discontinuation were few in number. These are presented in detail in Dr. Yancey's review. Abdominal pain and worsening JRA were the most common AEs leading to discontinuation. LFT abnormalities were defined in this study as AST or ALT greater than 3 X the upper limit of normal or 2X baseline if above the upper limit of normal and were present in 2% to 4% of patients across treatment groups, during the 12-week study. Three patients discontinued from the lower-dose rofecoxib group, one from the higher-dose rofecoxib group and none from the naproxen group due to LFT elevations during the 12-week study, and all elevations returned to normal following discontinuation of study drug. Two patients treated with rofecoxib discontinued the 52-

week open-label extension due to LFT elevations including one patient reported with the SAE of hepatitis A and one with the SAE of bronchitis also found to have hepatomegaly.

Adverse events occurred in 63% of all patients in the 12-week double-blind study, and 75% of patients during the 52-week extension. There were none reported during the pharmacokinetic studies. The AE profile during the 12-week study and 52-week extension was generally not unexpected in patients with JRA receiving NSAIDs and DMARDs and was similar across treatment groups. The most common AEs were abdominal pain, nausea, diarrhea, headache, upper respiratory infections, fever. In addition to the LFT abnormalities noted previously, there were a few additional LFT abnormalities noted in each treatment group. No elevations of creatinine were reported. There was no clear dose-response for the adverse events reported across the lower and higher-dose rofecoxib treatment groups.

Clinical Pharmacology and Biopharmaceutics

Four studies were submitted to provide pharmacokinetic information. Steady-state pharmacokinetic parameters of rofecoxib were characterized in patients ages 2 through 17 and compared to the steady-state PK in adult patients with rheumatoid arthritis (RA). Enrollment criteria in the three pediatric PK studies included patients with JRA ranging from 10 kg to 42 kg, with pauciarticular and polyarticular JRA. Dosing for the clinical efficacy trial was based on assumptions that the exposure-response relationship in pediatric patients was similar to healthy adults, in healthy adults was similar to adults with RA, and the exposure was dose-proportional across the effective dose range in patients with JRA and RA. Findings from the PK studies revealed that the clearance from adult RA patients was lower than normal adults by as much as 32% so that had dosing in the JRA efficacy trial would have been higher had this information been known earlier. Apparent oral clearance of rofecoxib increases with body weight and body surface area for all in JRA patients, and with increasing age for patients 2 years through 11 years old. Furthermore, clearance in JRA patients 12 to 17 years of age was comparable to healthy adults and so, higher than adults with JRA. The pharmacokinetic study results have been reviewed in detail by Dr. Lei Zhang.

Dosing and Administration

The higher-dose of rofecoxib during the clinical trial has sufficient evidence of efficacy based on non-inferiority to naproxen, without any notable difference in adverse event profile compared to the lower-dose rofecoxib and so, is recommended for use. The maximum dose of rofecoxib for treating the signs and symptoms of JRA is 25 mg/day. The dosing recommendation for patients between 2 years and 11 years of age weighing

between 10 kg and 42 kg is 0.6 mg/kg/day. For patients between 2 years and 11 years of age over 42 kg, and patients between 12 years and 17 years of age the dose is 25 mg/day.

Product Labeling

There were limitations in this pediatric development program. The efficacy trial was a non-inferiority design, just one clinical efficacy trial was performed, and the overall the number of patients studied was small. While sufficient evidence of efficacy was demonstrated for the purpose of establishing a pediatric indication for the treatment of the signs and symptoms of pauciarticular and polyarticular JRA in patients 2 years and older and who weigh over 10 kg, no comparative claim against naproxen can be supported. It is important to provide sufficient information in the package insert to describe the basis for the indication, but the specific identification of naproxen in the package insert would provide the basis for an implied claim of equivalence. Therefore, it is most prudent to describe the study and use the term 'active comparator' in place of 'naproxen'.

The patient package insert should be updated to reflect the new indication. Risk communication should be prioritized such that safety information is presented first. The Medication Guide format is recommended as the format for the patient package insert.

Discussion

The Sponsor has submitted four pharmacokinetic studies and one clinical efficacy study with an open-label extension in support of the efficacy and safety of rofecoxib for the treatment of juvenile rheumatoid arthritis. These studies fulfilled the requirements of the Pediatric Written Request. Adequate evidence of efficacy was demonstrated as non-inferiority of rofecoxib 0.6 mg/kg/day up to a maximum of 25 mg/day, to the active comparator, naproxen 15 mg/day. The non-inferiority study design was deemed acceptable for the clinical setting of JRA. The safety profile was similar across treatment groups and without unexpected findings in the JRA population relative to the adult RA population.

Negotiations took place between the Division and the Sponsor over the language of package insert and patient package insert. No agreement could be reached concerning references to the active comparator in the package insert. The Sponsor was unwilling to omit use of 'naproxen' to identify the active comparator in the absence of an a priori commitment to the nature of promotional activities that would include reference to naproxen. It is on this basis that an approvable action has been taken for this submission. The indication for the treatment of the signs and symptoms of polyarticular and pauciarticular juvenile rheumatoid arthritis in patients 2 years and older and who weigh over 10 kg is approvable, pending agreement on appropriate language in the package

insert. Additionally, the patient package insert does not currently adequately convey risk communication, the Medication Guide format and communication of safety concerns at the beginning of the document were rejected by the Sponsor.

Action recommended by the Division: Approvable

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V, CDER, FDA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

OFFICE DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301) 827-2040

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: August 5, 2004

DRUG: Vioxx (rofecoxib)

NDA: 21-042 (SE5-026)
21-052 (SE5-019)

SPONSOR: Merck & Co., Inc.

INDICATION: The treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis in patients 2 years and older and who weigh 10 kg or more

Merck & Co., Inc. submitted efficacy supplements for Vioxx™ (rofecoxib) for the indication of the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) to NDAs 21-042/S-026 (Tablets 12.5 mg and 25 mg) and 21-052/S-019 (Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL) on December 5, 2003. An Approvable action was taken on June 4, 2004. Although agreement was reached that the study submitted in support of efficacy demonstrated noninferiority to the comparator, agreement was not reached on the language to be added to the package insert describing the pediatric clinical trial. Agreement was also not reached on the Division's proposal to update the language and the organization of the patient package insert. As this was a pediatric efficacy supplement, upon taking an approvable action, the package was to go before the Pediatric Advisory Committee. However, as there was no disagreement over the scientific basis for a finding of noninferiority, and in consultation with the pediatric team, it was decided that if agreement on the language for the package insert and patient package insert could be reached with only a small amount of additional negotiation, it would not be necessary to go before the advisory committee.

The sponsor submitted a package insert and patient package insert on July 19, 2004. Following a discussion by telephone with the sponsor on July 29, 2004, agreement was reached and the final, agreed upon package insert and patient package insert were submitted on July 30, 2004. In particular, the description of the clinical trial in the package insert refers

to an [redacted] patient package insert, while not in Med Guide format, has been reorganized to emphasize important risk information.

Action recommended by the Division: Approval

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

CHEMISTRY REVIEW(S)

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, at the higher of two study doses, 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 of the higher of the two rofecoxib study doses demonstrate statistical non-inferiority to naproxen with an acceptable adverse event profile. The lower-dose rofecoxib failed to demonstrate non-inferiority to naproxen.

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 46.2%, 54.5% and 55.1% in lower-dose rofecoxib, 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, chronic low back pain, acute pain, and dysmenorrhea in the United States and, additionally, indicated for acute gouty arthritis and ankylosing spondylitis in Europe. 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) ≥ 0.50. 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%.

The Division specified in the pediatric WR, that a lower limit margin of the point estimate ≥ 0.50 (95% CI), was too low to support a finding of efficacy based on a non-inferiority trial design. This review was conducted using a lower limit margin of ≥ 0.75, employing this margin, as discussed below, only the higher-dose of rofecoxib achieved non-inferiority to naproxen.

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.* The lower-dose of rofecoxib achieved a point estimate of 0.81 (95% CI **0.61*** to 1.07, in a modified-intent-to-treat analysis, *regardless of*

completion status, and achieved a point estimate of 0.81 (95% CI, **0.61*** to 1.09), modified intent to treat, *responder and completer.* Therefore, since the lower limit of the point estimate (***bolded font**) was less than 0.75 in the lower-dose rofecoxib group, this dose was considered inferior to naproxen.

The proportion of patients who achieved the JRA DOI 30 criterion, MITT, *regardless of completion status*, over the 12-week study was 46.2%, 54.5% and 55.1% for the lower-dose rofecoxib, 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

) 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, chronic low back pain, acute pain, dysmenorrhea in the United States and, additionally, indicated for acute gouty arthritis and ankylosing spondylitis in Europe.

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 effica[illegible] 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 with a trial design of non-inferiority, the lower limit bound of ≥ 0.5 is not acceptable to obtain an indication.
- 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[a]	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)

[a] 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 3/109 (2.8%), 4/100 (4.0%) and 4/101 (4.0%), for the lower-dose rofecoxib, 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 [1]
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

[1] 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. The results in **Table 6** and **Figure 1** support the findings of the primary analysis. That is, the proportion of patients meeting the JRA DOI 30 criteria were similar among lower-dose rofecoxib, higher-dose rofecoxib, and naproxen treatment groups, and between-treatment comparisons met the predefined non-inferiority criteria (95% CI for ratio >0.5).

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
In Protocol 134/135, higher-dose rofecoxib demonstrated efficacy as non-inferiority to the active comparator naproxen, within the WR pre-specified lower limit* margin of 0.50 at the 95% confidence level. This Medical Reviewer notes that the Division clarified in the WR to the sponsor, that a point estimate lower limit margin of 0.50 was too wide to achieve an indication by non-inferiority. This review was conducted using a non-inferiority point estimate lower limit margin of ≥ 0.75, within which only 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.**)

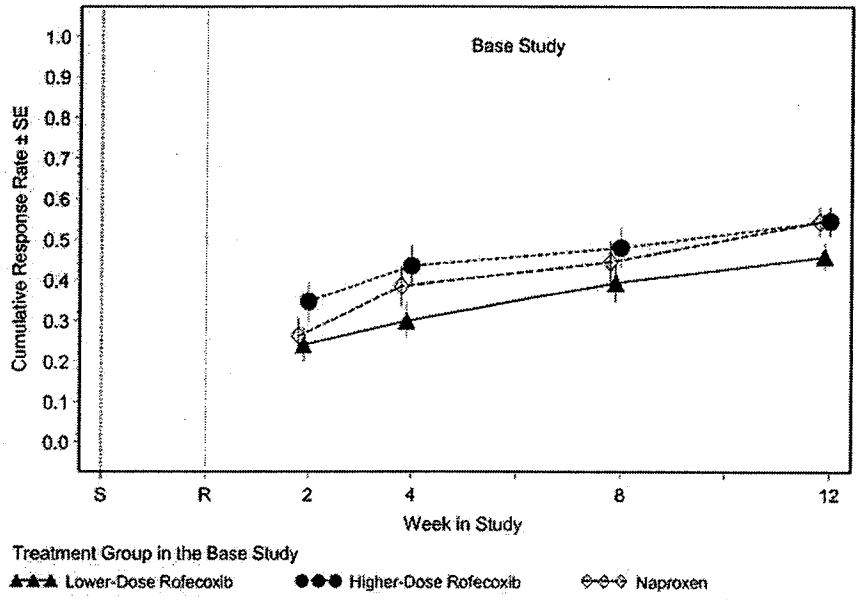
The lower-dose of rofecoxib did not achieve non-inferiority to naproxen by the lower limit of ≥ 0.75, lower limit was 0.81 95%CI (**0.61**, 1.07), in a modified-intent-to-treat analysis, *regardless of completion status*. Similarly, the lower-dose of rofecoxib did not achieve non-inferiority to naproxen, lower limit was 0.81 95%CI (**0.61**, 1.09), in a modified-intent-to-treat, *responder and completer*. 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. The composite endpoint of response to the JRA DOI 30 criteria did not demonstrate statistical significance between the higher-dose rofecoxib and the lower-dose rofecoxib.

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 (%)	
Lower-Dose Rofecoxib	49 /106 (46.2)	
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)
Lower Dose Rofecoxib vs. Naproxen	0.81 (0.61, 1.07)	-10.7 (-23.9, 2.5)
Higher Dose vs. Lower Dose Rofecoxib	1.21 (0.92, 1.60)	9.6 (-3.7, 22.8)
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
Lower-Dose Rofecoxib	48 /106 (45.3)	
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)
Lower Dose Rofecoxib vs. Naproxen	0.81 (0.61, 1.09)	-10.0 (-23.1, 3.1)
Higher Dose vs. Lower Dose Rofecoxib	1.24 (0.94, 1.64)	10.5 (-2.7, 23.7)

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. In the lower dose rofecoxib treatment group, fewer 12 year to 17 year olds responded to treatment, as defined by the JRA DOI 30 criteria. The point estimate of the ratio of response rates, relative to naproxen was **0.63,** close to the prespecified comparability bound, and the lower limit of the 95% CI was **0.4**, less than the prespecified bound of ≥ 0.5 and this Reviewer's lower limit bound of ≥ 0.75. This observation should be interpreted with caution because of the smaller sample size in this age group than that of the combined analysis of both age groups. 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 (%)	
Lower-Dose Rofecoxib	17 /43 (39.5)	
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)
Lower-Dose Rofecoxib vs. Naproxen	0.63 (0.40, 0.99)	-22.3 (-41.7, -2.9)
Higher-Dose vs. Lower-Dose Rofecoxib	1.35 (0.84, 2.19)	13.7 (-6.8, 34.2)
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
Lower-Dose Rofecoxib	17 /43 (39.5)	
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)
Lower-Dose Rofecoxib vs. Naproxen	0.65 (0.41, 1.04)	-20.0 (-39.3, -0.7)
Higher-Dose vs. Lower-Dose Rofecoxib	1.35 (0.84, 2.19)	13.7 (-6.8, 34.2)

† 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.

The ratio of response rates to the JRA DOI 30 primary efficacy endpoint for lower-dose rofecoxib versus naproxen, MITT analysis, *regardless of completion*, was estimated as 46.2% and 55.1%, respectively. Lower-dose rofecoxib was non-inferior to naproxen, point estimate of 0.81, 95% CI (**0.61**, 1.07). Using the ITT-LOCF population, the ratio of response rates to the JRA DOI 30 criterion were 45.3% and 53.5%, lower dose rofecoxib and naproxen, respectively. By the ITT-LOCF analysis, the point estimate was 0.81 95%CI (**0.61**, 1.09).

Using the per protocol analysis, lower dose rofecoxib versus naproxen using the responder rate to the JRA DOI 30, *regardless of completion status*, was estimated to be 0.96 (95%CI **0.73**, 1.25); *responder and completer status*, per protocol analysis, lower dose rofecoxib versus naproxen, responder rate was estimated to be 0.94, (95% CI **0.70**,

1.26). According to the sponsor, the point estimates of the ratio of response rates to the JRA DOI 30 show that approximately 20% fewer patients responded to the lower dose rofecoxib than to naproxen.

Secondary Endpoints

The proportion of JRA patients demonstrating improvement from baseline in the parent/ patient assessment of overall well-being was 74.3%, 76.0% and 73.0%, lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. In the analysis of change from baseline in the individual components of the JRA DOI 30, comparison of the parent/patient's assessment of overall well-being favored higher-dose rofecoxib relative to naproxen by a small numeric difference; the treatment difference was 1.02 joints (95% CI: 0.14, 1.89). 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[3] (%)	
Lower-Dose Rofecoxib	81 /109 (74.3)	
Higher-Dose Rofecoxib	76 /100 (76.0)	
Naproxen	73 /100 (73.0)	
Between-Group Comparison	**Relative Risk[5] (95% CI)**	**Difference[4] (95% CI)**
Higher-Dose Rofecoxib vs. Naproxen	1.04 (0.89, 1.22)	3.1 (-8.8, 15.0)
Lower-Dose Rofecoxib vs. Naproxen	1.01 (0.86, 1.20)	1.0 (-10.9, 12.8)
Higher-Dose vs. Lower-Dose Rofecoxib	1.03 (0.87, 1.21)	2.2 (-9.5, 14.0)

[3] 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.
[4] From Mantel-Haenszel estimate with protocol, age group, and joint involvement as stratification factors.
[5] From the normal approximation for a Cochran-Mantel-Haenszel (CMH) weighted average of the differences over all strata.

The proportion of patients demonstrating improvement from baseline in the parent/patient assessment of pain was most improved in lower-dose rofecoxib and higher dose rofecoxib treatment groups compared to naproxen. The mean change from baseline for lower-dose rofecoxib, higher-dose rofecoxib and naproxen was -13.07, -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
Lower-Dose Rofecoxib	109	42.08	29.01	-13.07	20.80	-12.50	(-15.98, -9.02)
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
Lower-Dose Rofecoxib vs. Naproxen	-4.07	(-8.95, 0.80)	0.101
Higher-Dose vs. Lower-Dose Rofecoxib	-0.62	(-5.48, 4.25)	0.803

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.

Using the key primary and secondary endpoints, see **Tables 10** and **11**, demonstrate that higher-dose rofecoxib versus naproxen showed better response rates than did lower-dose rofecoxib versus naproxen; however, these results were not statistically significant.

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)	0.98 (0.76, 1.26)
Proportion of Patients Meeting JRA30 Response Criteria (Responder and Completer)	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	-3.52 (-8.14, 1.10)
Investigator Global Assessment of Disease Activity	-1.21 (-4.80, 2.37)
Functional Ability	-0.03 (-0.12, 0.07)
Number of Joints With Active Arthritis	0.37 (-0.48, 1.22)
Number of Joints With Limited Range of Motion	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.

Table 11. 12-Week Study, Analysis of Primary and Secondary Key Endpoints: Lower-Dose Rofecoxib versus Naproxen (This table is from the sponsor's submission, Table 2.5:3)

JRA 30 Core Set of Variables	Lower-Dose Rofecoxib versus Naproxen
Primary Endpoint: Ratio of Response Rates (95% CI)†	
Proportion of Patients Meeting JRA30 Response Criteria (Regardless of Completion Status)	0.81 (0.61, 1.07)
Proportion of Patients Meeting JRA30 Response Criteria (Responder and Completer)	0.81 (0.61, 1.09)
Key Secondary Endpoint (95% CI)†	
Proportion of Patients With Improvement From Baseline in Parent/Patient's Assessment of Overall Well-Being	1.01 (0.86, 1.20)
Secondary Endpoint Not Included in JRA30 Core Set: LS Mean Difference in Change From Baseline (95% CI)‡	
Parent/Patient's Global Assessment of Pain	-4.07 (-8.95, 0.80)
JRA Core Set: LS Mean Difference in Change From Baseline (95% CI)‡	
Parent/Patient's Assessment of Overall Well-Being	-3.01 (-7.53, 1.50)
Investigator Global Assessment of Disease Activity	-0.40 (-3.91, 3.12)
Functional Ability	0.01 (-0.09, 0.10)
Number of Joints With Active Arthritis	0.38 (-0.45, 1.21)
Number of Joints With Limited Range of Motion	1.18 (0.32, 2.03)
LS Mean Ratio (95% CI)§	
Erythrocyte Sedimentation Rate (ESR)	1.00 (0.84, 1.18)

† 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.

Between Group Comparison: Higher-Dose versus Lower-Dose Rofecoxib

Between-group comparison in all efficacy endpoints, demonstrates that higher-dose rofecoxib has a better ratio of response to the JRA DOI 30 than does lower-dose rofecoxib. See **Table 12**.

Table 12. 12-Week Study, Protocol 134/135, Summary, Between Group Comparison of Treatment Effects: Higher-Dose Rofecoxib versus Lower-Dose Rofecoxib
(This Table is from the sponsor's submission, Table 39, Section 7.4, page 113 of 2398.)

Primary Endpoint		
	Relative Risk† (95% CI)	Difference‡ (95% CI)
JRA 30 Responder Index: Regardless of Completion Status	1.21 (0.92, 1.60)	9.6 (-3.7, 22.8)
JRA 30 Responder and Completer	1.24 (0.94, 1.64)	10.5 (-2.7, 23.7)
Key Secondary Endpoint		
	Relative Risk† (95% CI)	Difference‡ (95% CI)
Proportion of Patients Demonstrating Improvement from Baseline in Parent/Patient's Assessment of Overall Well-Being	1.03 (0.87, 1.21)	2.2 (-9.5, 14.0)
Other Secondary Endpoints		
	Difference§ (95% CI)	
Parent/Patient's Global Assessment of Pain‖	-0.62 (-5.48, 4.25)	
Discontinuation Due to Lack of Efficacy	1.25 (-3.67, 6.17)	
JRA 30 Core Set of Variables		
Parent/Patient's Assessment of Overall Well-Being‖	-0.51 (-5.00, 3.98)	
Investigator Global Assessment of Disease Activity‖	-0.82 (-4.33, 2.69)	
Functional Ability (CHAQ)‖	-0.03 (-0.13, 0.06)	
Number of Joints With Active Arthritis‖	-0.01 (-0.85, 0.82)	
Number of Joints With Limited Range of Motion‖	-0.16 (-1.01, 0.70)	
Erythrocyte Sedimentation Rate¶	0.91 (0.77, 1.08)	

† 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.
§ Negative values in the difference indicate greater improvement from baseline for the higher-dose rofecoxib compared to the lower-dose rofecoxib treatment group.
‖ The difference in Least Squares mean time-weighted average change from baseline using an Analysis of Covariance including terms for treatment group, protocol stratum, joint involvement stratum (pauci-, poly-articular), age group, and baseline value as a 1-degree-of-freedom covariate.
¶ LS mean ratio between treatments (ratio of on-treatment/baseline ratio). Values less than 1 indicate greater efficacy for the higher-dose rofecoxib as compared to the lower-dose rofecoxib treatment group.
JRA = Juvenile Rheumatoid Arthritis.

Additional Analyses

Primary and Secondary Endpoint Comparison by *Age Group*

In support of the higher-dose rofecoxib versus lower-dose rofecoxib, using the JRA DOI 30 as the primary endpoint, younger patients, 2 years to 11 years, and older patients, 12 years to 17 years of age, treated with lower-dose rofecoxib demonstrate a smaller efficacy response to the JRA DOI 30 than do the same age-matched JRA patients, in both age groups, treated with the higher-dose rofecoxib. 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 (%)	
Lower-Dose Rofecoxib	32 /63 (50.8)	
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)
Lower Dose Rofecoxib vs. Naproxen	0.96 (0.67, 1.38)	-2.0 (-20.0, 15.9)
Higher Dose vs. Lower Dose Rofecoxib	1.14 (0.81, 1.59)	6.7 (-10.6, 24.0)
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
Lower-Dose Rofecoxib	31 /63 (49.2)	
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)
Lower Dose Rofecoxib vs. Naproxen	0.95 (0.65, 1.38)	-2.7 (-20.5, 15.1)
Higher Dose vs. Lower Dose Rofecoxib	1.17 (0.83, 1.65)	8.3 (-9.0, 25.5)

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 (%)	
Lower-Dose Rofecoxib	17 /43 (39.5)	
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)
Lower-Dose Rofecoxib vs. Naproxen	0.63 (0.40, 0.99)	-22.3 (-41.7, -2.9)
Higher-Dose vs. Lower-Dose Rofecoxib	1.35 (0.84, 2.19)	13.7 (-6.8, 34.2)
JRA 30 Responder and Completer (Secondary)[‖]		
Treatment	Frequency (%)	
Lower-Dose Rofecoxib	17 /43 (39.5)	
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)
Lower-Dose Rofecoxib vs. Naproxen	0.65 (0.41, 1.04)	-20.0 (-39.3, -0.7)
Higher-Dose vs. Lower-Dose Rofecoxib	1.35 (0.84, 2.19)	13.7 (-6.8, 34.2)

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

In patients 2 to 11 years old, both rofecoxib treatment groups had greater improvement from baseline in parent/patient's global assessment of pain than the naproxen treatment group. For patients 12 to 17 years old, the lower-dose rofecoxib treatment group had a smaller treatment effect than the naproxen treatment group in the number of joints with active arthritis. 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[†] (%)	
Lower-Dose Rofecoxib	50 /65 (76.9)	
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)
Lower-Dose Rofecoxib vs. Naproxen	1.08 (0.87, 1.34)	5.7 (-9.9, 21.4)
Higher-Dose vs. Lower-Dose Rofecoxib	0.99 (0.80, 1.21)	-1.1 (-16.2, 14.0)

† 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[†] (%)	
Lower-Dose Rofecoxib	31 /44 (70.5)	
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)
Lower-Dose Rofecoxib vs. Naproxen	0.93 (0.71, 1.21)	-5.6 (-23.9, 12.7)
Higher-Dose vs. Lower-Dose Rofecoxib	1.10 (0.84, 1.45)	7.2 (-11.5, 26.0)

† 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*

The secondary endpoint parent/patient global assessment of pain by age demonstrated slightly higher numerical response with higher-dose rofecoxib in children 2 years to 11 years old, treated with higher-dose rofecoxib compared to treatment lower-dose rofecoxib and naproxen. There is smaller difference in the 12 year to 17 year old patients, across the three treatment groups. 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
Lower-Dose Rofecoxib	65	38.66	25.86	-12.80	18.57	-13.98	(-18.26, -9.70)
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
Lower-Dose Rofecoxib vs. Naproxen	-8.51	(-14.81, -2.22)	0.008
Higher-Dose vs. Lower-Dose Rofecoxib	0.40	(-5.76, 6.56)	0.899

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
Lower-Dose Rofecoxib	44	47.14	33.66	-13.48	23.93	-9.71	(-15.54, -3.87)
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
Lower-Dose Rofecoxib vs. Naproxen	1.78	(-5.99, 9.55)	0.652
Higher-Dose vs. Lower-Dose Rofecoxib	-2.09	(-10.04, 5.87)	0.604

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
In analysis of the secondary efficacy endpoint subgroups, lower-dose rofecoxib was inferior compared to naproxen by the pre-specified margin of 0.50 percent at the lowest 95% confidence interval in the following categories: Polyarticular disease, males; 12 years to 17 years; Tanner Stage 2, 3, 4 and 5; Multi-racial; Duration of JRA < 3 years; Erythrocyte Sedimentation Rate 0 to 20; Methotrexate user; Corticosteroid user; DMARD user; Naproxen non-users and NSAID non-users. Similarly, higher-dose rofecoxib was inferior compared to naproxen by the pre-specified margin of 0.50 percent at the lowest 95 % confidence interval in the following categories: Males; NSAID non-users; Corticosteroid user and Tanner Stage 3 and 4.

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***

Dose Groups	Bodyweight Sub-Group (Kg)	Age (Years) n, Mean (Min, Max)	Number of Patients	Relative Risk (95% CI)
6.1.4 Assuming missing value as missing				
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)
Lower Dose Rofecoxib vs. Naproxen	All Bodyweight Group	204, 10.25 (2.00, 17.00)	49/106, 54/98	0.84 (0.63, 1.10)
Lower Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	37, 4.24 (2.00, 7.00)	11/21, 9/16	0.93 (0.49, 1.92)
Lower Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	83, 9.39 (4.00, 17.00)	21/46, 19/37	0.89 (0.56, 1.43)
Lower Dose Rofecoxib vs. Naproxen	Bodyweight>= 40	84, 13.75 (9.00, 17.00)	17/39, 26/45	0.75 (0.47, 1.17)
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)
Lower Dose Rofecoxib vs. Naproxen	All Bodyweight Group	210, 10.18 (2.00, 17.00)	49/109, 54/101	0.84 (0.63, 1.11)
Lower Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	39, 4.20 (2.00, 7.00)	11/22, 9/17	0.94 (0.49, 1.96)
Lower Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	86, 9.40 (4.00, 17.00)	21/48, 19/38	0.88 (0.55, 1.42)
Lower Dose Rofecoxib vs. Naproxen	Bodyweight >=40	85, 13.72 (9.00, 17.00)	17/39, 26/46	0.77 (0.48, 1.20)

Based on the additional secondary endpoint analyses, this Medical Reviewer concludes that the parent/ patient's overall assessment of well-being demonstrated numerically better response with higher-dose rofecoxib than lower-dose rofecoxib and was comparable to naproxen. 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, 2.8, 4.0 and 4.0%, lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively.

Additional between-group comparison by age, based on the analysis of primary efficacy endpoint, demonstrated that in 2 year to 11 year old patients versus 12 year to 17 year old patients, regardless of completion status and responder and completer status, only higher-dose rofecoxib in 2 year to 11 year olds achieves non-inferiority at the point estimate lower limit of ≥ 0.75.

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	5.0-mg/mL rofecoxib suspension	None
Naproxen	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	Rofecoxib 25-mg tablets	None
Naproxen	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. These results trended similarly to the efficacy results of the 12-week study favoring higher-dose rofecoxib. 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 only the higher study dose of rofecoxib, 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. Higher-dose rofecoxib had numerically better treatment effect than lower-dose rofecoxib in all efficacy endpoints, though not statistically significantly different.

Secondary endpoint efficacy analysis of the parent/ patient's overall assessment of well-being demonstrated numerically better response with higher-dose rofecoxib than lower-dose rofecoxib and comparability to naproxen. 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.**

Table 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 119; injection of triamcinolone hexacetomide day 120; recovered, d/c home
AN 634, 9 yrs, Male	Higher-dose rofecoxib, 0.6 mg/kg	Worsening JRA; day 93; Diagnosed uveitis; hospitalization day 105; concomitant meds: MTX	Completed study medication; multiple joint injections; Rx naproxen; increased MTX dose from 10mg/kg/wk to 15mg/kg/wk; recovered day 125, 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 7. 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	44/ 160	27.5%	
Naproxen	26/ 67	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	2/160	1.3%	
Naproxen	5/67	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[f]	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)

[f] 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 higher of two rofecoxib study doses, 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. The lower of the two rofecoxib doses, [illegible] once per day, did not achieve efficacy within this margin. Therefore, only the higher dose is recommended for approval for the proposed indication.

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 46.2, 54.5 and 55.1% in lower-dose rofecoxib, 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.
- Non-approval of the lower of the two rofecoxib doses, [illegible] ice per day, as this dose did not achieve efficacy according to this review at the lower limit of ≥ 0.75 for a non-inferiority trial design to the extent of the higher dose rofecoxib.

- 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

<u>Protocol 134/135</u>
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.

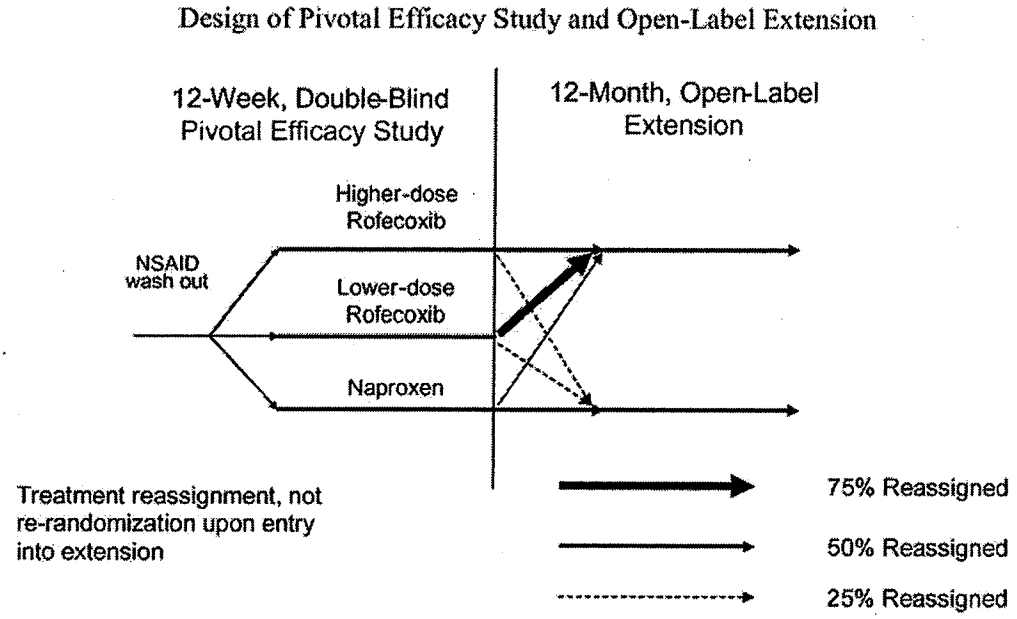
Study Medication/s
Ongoing stable DMARD therapies were permitted, but only if doses were anticipated to remain unchanged over the study course. Eligible patients underwent a brief washout of prior NSAID therapy and were assigned to 1 of 3 treatment groups, as noted if figure 1, in approximately equal 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[4]
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[7]	• Yes • No
Baseline disease-modifying anti-rheumatic drugs (DMARD) user[5]	• Yes • No
Prior naproxen user[8]	• 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 [illegible] 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 above 0.5. A step-down procedure will be employed to compare each dose with naproxen. First, the CI for the higher rofecoxib dose versus naproxen will be compared to 0.5, and only if above 0.5 will the CI for the lower rofecoxib dose be compared to 0.5.

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 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.

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/s/

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

review vioxx ped rheum supplements

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Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-042/SE5
Drug Name:	Vioxx™ (Rofecoxib Tablets)
Indication(s):	Juvenile Rheumatoid Arthritis
Applicant:	Merck and Company Inc. Rahway NJ 07065-0900
Date (s):	Submitted: December 5, 2003 Received: December 5, 2003 Reviewed: May 19, 2004
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	M. Atiar Rahman, Ph.D. (HFD-725)
Concurring Reviewer:	Stan Lin, Ph.D. (HFD-725)
Medical Division:	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Carolyn Yancey, M.D. (HFD-550)
Project Manager:	Barbara Gould (HFD-550)
Keywords:	NDA review, Clinical studies, Juvenile Rheumatoid Arthritis, Non-inferior

Table of Contents

1 Executive Summary 4
1.1 Conclusions and Recommendations 4
1.2 Brief Overview of Clinical Studies 4
1.3 Statistical Issues and Findings 5
2 Introduction 5
2.1 Overview 5
2.2 Data Sources 5
3 Statistical Evaluation 5
3.1 Evaluation of Efficacy 5
3.1.1 Study # 143/135 (Phase-3) 5
3.1.1.1 Design and Objectives 5
3.1.1.2 Efficacy Endpoint 6
3.1.1.3 Patient Analyzed 7
3.1.1.4 Disposition of Patients, Demography 7
3.1.1.5 Sponsor's Analysis of Primary Efficacy Data 7
3.1.1.6 Sponsor's Results and Conclusions 8
3.1.1.7 Reviewer's analyses and Conclusions 9
3.2 Evaluation of Safety 9
3.2.1 Sponsor's Analysis of Safety Data 9
3.2.2 Reviewer's Analysis of Safety Data 10
4 Findings in Special/Subgroup Populations 11
4.1 Reviewer's analysis of subgroup population: 11
5 Summary and conclusions 12
5.1 Statistical issues and collective evidence 12
5.2 Conclusions and recommendations 12
6 Appendix-1 14
6.1 Table 1: Patient Disposition 14
6.2 Table 2: Baseline Demographic Characteristics 14

6.3 Table 3: Endpoints and Their Statistical analyses 15
6.4 Table 4: Sponsor's analyses of Primary Efficacy Variables 16
6.5 Table 5: Sponsor's analyses of Primary Efficacy Variables 17
6.6 Table 6: parent/patient's assessment of overall well-being 18
6.7 Table 7: patient's global assessment of pain 19
6.8 Table 8: Sponsor's analyses of Safety Data 19
6.9 Table 9: Subgroup Analysis of JRA 30 Responder Rates by AGE 20
6.10 Table 10: Subgroup Analysis of JRA 30 Responder Rates by Bodyweight 21

7 Appendix- 2 22
7.1 Statistical Analysis Plan 22

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this submission the sponsor included report of a Phase 3 study (Protocol134/135). This was a 12 week, double blind, double dummy, active comparator controlled study in 2 to 17 years old juvenile rheumatoid arthritis patients. There were three treatment groups namely, (1) lower dose rofecoxib- 0.3 mg/kg/day for 2 to 11 year old patients (not to exceed 12.5 mg/day), or 12.5 mg daily for 12 to 17 year old patients; (2) higher dose rofecoxib- 0.6 mg/kg/day for 2 to 11 year old patients (not to exceed 25 mg/day), or 25 mg daily for 12 to 17 year old patients; (3) naproxen- targeted to 15 mg/kg/day. The primary objectives of this study were to examine the therapeutic effects and safety of two doses of rofecoxib and to show the non-inferiority of rofecoxib compared to naproxen.

The primary efficacy endpoint was proportion of patients in the ITT population meeting the JRA 30 criteria. The non-inferiority is claimed if the 95% confidence interval on the relative risk (ratio of percent of patients meeting the JRA 30 criteria) of rofecoxib vs. naproxen was entirely above 0.5.

The results from both ITT and completers analyses showed that for both higher dose of rofecoxib vs. naproxen, and lower dose vs. naproxen the 95% CIs on risk ratios were above 0.5.

However, the Division considered the non-inferiority margin of 0.5 as too wide. In ITT population the lower limits of the 95% CIs were 0.76 for higher dose rofecoxib vs. naproxen and 0.61 for lower dose rofecoxib vs. naproxen. Therefore, for non-inferiority margin greater than 0.61 the lower dose of rofecoxib would fail to establish non-inferiority to Naproxen. The medical officer's preference of non-inferiority margin is 0.75 (see medical officer's review). Also, in many subgroups the low dose group did not establish non-inferiority even with a non-inferiority margin of 0.5.

In light of the above discussion and in consultation with the medical reviewer, this reviewer concludes that rofecoxib dose of 0.3 mg/kg/day did not show non-inferiority in treatment effect measured in JRA 30 when compared to naproxen.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission the sponsor included report of a Phase 3 study (Protocol 134/135). This was a 12 week, double blind, double dummy, active comparator controlled study in 2 to 17 year old Juvenile Rheumatoid Arthritis (JRA) patients. Within each study site, allocations were stratified for age: 2 to 11 years and 12 to 17 years, and by pauci articular and poly articular disease. In each age group, patients were allocated to receive 1 of the 3 treatments: (1) lower dose rofecoxib, 0.3 mg/kg/day for 2 to 11 year old patients (not to exceed 12.5 mg/day), or 12.5 mg daily for 12 to 17 year old patients; (2) higher dose rofecoxib, 0.6 mg/kg/day for 2 to 11 year old patients (not to exceed 25 mg/day), or 25 mg daily for 12 to 17 year old patients; (3) naproxen, targeted to 15 mg/kg/day. The 2 to 11 year old patients received suspension formulations, and the 12 to 17 year old patients received tablets. Clinical assessments took place at pre-study screening, randomization, and after 2, 4, 8, and 12 weeks of treatment. In addition, a 14 day post-study follow up was required of all patients after discontinuation. The primary objectives of this study were (1) to examine the therapeutic effects of 2 dose strengths of rofecoxib, taken as oral suspension, in 2 to 11 year old JRA patients (0.3, and 0.6 mg/kg/day); (2) to examine the therapeutic effects of 2 dose strengths of rofecoxib, taken as tablets, in 12 to 17 year old JRA patients (12.5 mg 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 of naproxen for treatment of JRA, and compare rofecoxib with naproxen (non-inferiority); and (5) To examine treatment effects in patients with pauci articular and poly articular disease, respectively.

1.3 STATISTICAL ISSUES AND FINDINGS

In sponsor's analysis non-inferiority of a dose of rofecoxib to naproxen was claimed if the 95% CI on the risk ratio for that dose vs. naproxen was above 0.5. The Division considers the proposed non-inferiority margin of 0.5 (preservation of 50% of the effect of naproxen) as unacceptably wide. The determination of whether the efficacy of rofecoxib is comparable or not to naproxen in the JRA population, was to be a review issue.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA the sponsor submitted data of a Phase 3 study (Protocol134/135) to support their claim that the use of Vioxx is safe and efficacious for the treatment of Juvenile Rheumatoid Arthritis and that Vioxx is non-inferior in efficacy to Neproxen.

2.2 DATA SOURCES

The submission was both electronic and hard copy. Submitted data were stored in folder \\Cdsesub1\n21042\S_026\2003-12-05\Crt of FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limit.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY # 143/135 (PHASE-3)

Title: "A 12 Week Active Comparator Controlled Trial to Evaluate the Efficacy and Safety of rofecoxib for Treatment of Juvenile Rheumatoid Arthritis"

3.1.1.1 Design and Objectives

This was a 12 week, double blind, double dummy, active comparator controlled study in 2 to 17 year old JRA patients. Within each study site, allocations were stratified for age: 2 to 11 years and 12 to 17 years, and by pauci articular and poly articular disease. In each age group, patients were allocated to receive 1 of the 3 treatments: (1) lower dose rofecoxib 0.3 mg/kg/day for 2 to 11 year old patients (not to exceed 12.5 mg/day), or 12.5 mg daily for 12 to 17 year old patients; (2) higher dose rofecoxib, 0.6 mg/kg/day for 2 to 11 year old patients (not to exceed 25 mg/day), or 25 mg daily for 12 to 17 year old patients; and (3) naproxen, targeted to 15 mg/kg/day. The 2 to 11 year old patients received suspension formulations, and the 12 to 17 year old patients received tablets. Clinical assessments took place at pre-study screening, randomization, and after 2, 4, 8, and 12 weeks of treatment. In addition, a 14 day post-study follow up was required of all patients after discontinuation. The primary objectives of this study were (1) to examine the therapeutic effects of 2 dose strengths of rofecoxib, taken as oral suspension, in 2 to 11 year old JRA patients (0.3 mg/kg/day, not to exceed 12.5 mg, and 0.6 mg/kg/day, not to exceed 25 mg); (2) to examine the therapeutic effects of 2 dose strengths of rofecoxib, taken as tablets, in 12 to 17 year old JRA patients (12.5 mg 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 of rofecoxib for treatment of JRA, and compare to naproxen (non-inferiority); and (5) to examine treatment effects in patients with pauci articular and poly articular disease, respectively.

Eligible patients underwent a brief washout of prior NSAID therapy and were assigned to 1 of the 3 treatment groups, in approximately equal proportions. 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. The primary efficacy timepoint was Week 12.

A second phase of this study was a 12-month open label, active comparator controlled extension of treatment phase (pivotal study). The extension phase had two treatment groups, namely higher dose rofecoxib (0.6 mg/kg to a maximum of 25 mg once daily) and naproxen (15 mg/kg in 2 divided dose). There were 227 patients in the extension phase. In the extension phase some reassignments of patients in the treatment phase were performed following a randomization scheme prepared prior to randomization to treatment. Seventy five percent (75%) of patients in the lower rofecoxib dose group in the treatment phase were reassigned to higher dose rofecoxib and 25% were reassigned to naproxen. Fifty percent (50%) of the naproxen treated patient were reassigned to higher dose rofecoxib and 25% of the higher dose rofecoxib patients were reassigned to naproxen group. A schematic figure of this reassignment is given in Appendix-1.

Sample Size: In the protocol the sponsor stated "The sample size n=75 per dose group has at least 90% power to yield the 95% CI on the ratio of percent of patients improved greater than 0.5, if the true rates are equal for rofecoxib and naproxen and exceed 40%." However, in the actual study the sponsor recruited about 100 patients per treatment group. In their final report the sponsor mentioned "... the sample size of n=100 per dose group had 99% power to yield the 95% CI on the ratio of JRA 30 response rate greater than 0.5, if the true rates are equal for rofecoxib and naproxen and exceed 40%."

3.1.1.2 Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients meeting the JRA 30 criteria[1]. 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 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

[1] As a result of correspondence with the agency, an amendment was done when the primary efficacy endpoint was changed from improvement in Patient/Parents assessment of overall well being to the JRA 30 (12/06/2001 Written Request and its 5/14/2003 Amendment). The JRA 30 responder criteria were derived from a core set of 6 outcome variables for the assessment of children with JRA. Developed for assessment of impact of disease modifying anti rheumatic drug (DMARD) therapy on disease, improvement in patients with JRA was defined as an at-least 30% improvement from baseline in any 3 of the 6 variables in the core set, with not more than 1 of the remaining variables worsened by more than 30%. The variables included in the core set were: (1) investigator global assessment of disease activity; (2) parent/patient's global assessment of overall well being; (3) functional ability; (4) number of joints with active arthritis; (5) number of joints with limited range of motion, and (6) ESR. In addition to assessment of disease activity, an assessment of the patient's pain was conducted using the Patient's Global Assessment of Pain.

3.1.1.3 Patient Analyzed

Modified Intent-to-Treat population: Primary efficacy population was modified intention-to-treat (MITT) population, defined as all patients with a baseline and at least one on treatment-period measurement.

Safety population: MITT population was also used for safety analysis.

Reviewer's comment: For safety analysis all randomized who took one dose of study drug should be more appropriate.

Per Protocol population: The PP analysis population excluded patients or data points with clinically important protocol deviations based on pre-specified criteria.

Patients with any of the following were excluded from the PP analysis:

1. Parent/patient's assessment of overall well being (VAS) was >90 mm at the screening visit.
2. Parent/patient's assessment of overall well being (VAS) was <10 mm at allocation.
3. Patient had fewer than 1 active joint at allocation.
4. Patient had any inflammatory joint disease, other than JRA, that confounded collection of efficacy data.

3.1.1.4 Disposition of Patients, Demography

Disposition of ITT patients and their baseline characteristics are given in Table 1 and Table 2, respectively in Appendix-1. A total of 310 subjects were treated and post-studied, including 109 in rofecoxib 0.3 mg/kg group, 100 in rofecoxib 0.6 mg/kg group, and 101 Naproxen 15 mg/kg group. A total of 46 subjects (15, 22, and 9 in rofecoxib 0.3 mg/kg, rofecoxib 0.6 mg/kg, and Naproxen groups, respectively) were between 2-4 years of age, while a total of 135 subjects (50, 38, and 47 in rofecoxib 0.3 mg/kg, rofecoxib 0.6 mg/kg, and Naproxen groups, respectively) were between 5-11 years of age. Overall about 19% completed the study (24%, 18%, and 14% in rofecoxib 0.3 mg/kg, rofecoxib 0.6 mg/kg, and Naproxen groups, respectively). Most subjects dropped out due to lack of efficacy. The treatment groups were generally comparable with respect to demographic and baseline characteristics. The majority of subjects were female (73.2%) and Caucasian (72.6%) with a mean age of 9.9 years.

3.1.1.5 Sponsor's Analysis of Primary Efficacy Data

The statistical analysis plan, as was described in the protocol, is given in Appendix-2. The study hypotheses was that the proportion of patients that demonstrated improvement, defined as meeting JRA 30 criteria, will be similar between rofecoxib and naproxen treatment groups. This hypothesis was assessed by the 95% CI on the relative risk (ratio of percent of patients meeting the JRA 30 criteria) of rofecoxib versus naproxen, calculated using the Mantel-Haenszel estimate with protocol, joint involvement and age group as stratification factors. If the confidence interval was entirely above 0.5[2], it was concluded that efficacy of rofecoxib was non-inferior to that of naproxen.

---

[2] In February 27, 2003 the sponsor submitted the data analysis plan for Study P134/135. In April 20, 2003 the Division sent comments to the sponsor regarding the primary population for analysis and margin of comparability chosen for the study. In those comments the Division considered the proposed non-inferiority margin of 0.5 (preservation of 50% of the effect of naproxen) as unacceptably wide. The determination of whether the efficacy of rofecoxib is comparable or not to naproxen in the JRA population was to be a review issue.

An analysis of covariance (ANCOVA) model, with treatment, protocol, joints involvement, age group, and baseline value as factors 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 also done through graphical presentation of the LS mean changes from baseline. The proportion of patients discontinuing test therapy due to lack of efficacy was assessed using the Fisher's exact test.

The therapeutic effect of each dose of rofecoxib was assessed in 2 to 11 year old JRA patients by the ratio of percent of patients meeting the JRA 30 criteria (each dose vs. naproxen) and its associated 95% CI, stratified by protocol and joint involvement. A similar assessment was used for the proportion of patients that demonstrate improvement from baseline in parent/patient's assessment of overall well being. In addition, the comparisons of therapeutic effect between treatments for other efficacy endpoints in 2 to 11 year old JRA patients were assessed by the least squares (LS) mean changes from baseline and their associated 95% CIs, stratified by protocol and joint involvement.

The therapeutic effect of each dose of rofecoxib was assessed in 12 to 17 year old JRA patients by the ratio of percent of patients meeting the JRA 30 criteria (each dose versus naproxen) and its associated 95% CI, stratified by protocol and joint involvement. Similar assessment was used for the proportion of patients that demonstrate improvement from baseline in parent/patient's assessment of overall well being. In addition, the comparisons of therapeutic effect between treatments for other efficacy endpoints in 12 to 17 year old JRA patients were assessed by the LS mean changes from baseline and their associated 95% CIs, stratified by protocol and joint involvement.

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 except for the longitudinal graphs.

A corroborative per-protocol (PP) analysis was also performed for the primary endpoint. The PP analysis population excluded patients or data points with clinically important protocol deviations based on pre-specified criteria.

A complete list of statistical methods used by the sponsor to analyze the primary and secondary efficacy endpoints are summarized in Table 3 in Appendix 1.

3.1.1.6 Sponsor's Results and Conclusions

Results of sponsor's analysis of primary efficacy endpoints

Results of sponsor's analysis of primary efficacy variable are given in Table 4 in Appendix 1. The proportions of patients in MITT population, meeting the JRA 30 criteria regardless of completion status over the 12 week study were 0.46, 0.55, and 0.55 in lower-dose rofecoxib, higher dose rofecoxib, and naproxen treatment groups, respectively. The 95% CI on relative risk of higher dose rofecoxib to naproxen was 0.76 to 1.26, that of lower dose rofecoxib to naproxen was 0.61 to 1.07. Thus, the JRA 30 response rate of both higher and lower doses rofecoxib were non-inferior to that of naproxen as assessed by the 95% CI on relative risk (i.e. the 95% CIs were entirely above 0.5).

However, there was a trend to reduced efficacy with lower-dose rofecoxib as suggested by a numerically smaller proportion of patients meeting the JRA 30 criteria than higher dose rofecoxib.

Analysis of proportions of patients meeting the JRA 30 criteria in completers showed similar results. Additionally, the proportion of patients meeting the JRA 30 criteria, based on the time-weighted average up to each time point were similar throughout the base study. Results from the per-protocol population for the primary endpoint corroborated those from the MITT population as shown in Table 5 in Appendix 1.

Results of sponsor's analysis of secondary efficacy endpoints

Sponsor's analysis results of the key secondary endpoint, the proportion of patients with improvement from baseline in parent/patient's assessment of overall well being are given in Table 6 in Appendix 1. For, all 3 treatment groups showed similar treatment effect of 74.3%, 76.0%, and 73.0%, respectively. Sponsor's analysis results of patient's global assessment of pain are given in Table 7 in Appendix 1. Results showed that both the lower dose and higher dose rofecoxib treatment had numerically greater improvement than naproxen treatment. The mean change from baseline was –13.07, -13.61 and –9.11 respectively. The discontinuation rates due to lack of efficacy were similar among 3 treatment groups (2.8, 4.0, and 4.0%, respectively). For the JRA 30 core set of endpoints, all 3 treatment groups demonstrated similar treatment effect except for the number of joints with limited range of motion. Naproxen had significantly greater improvement from baseline in number of joints with limited range of motion than rofecoxib treatment groups. However, a similar pattern of difference, although not statistically significant, in the opposite direction was observed for parent/patient global assessment of well being, where it was analyzed as a continuous, rather than a dichotomous variable.

3.1.1.7 Reviewer's analyses and Conclusions

In order to verify sponsor's results, this reviewer recalculated the confidence intervals for the primary efficacy variable. This reviewer's results confirm sponsor's results.

The analysis results from both ITT and completers showed that for both high dose of rofecoxib vs. naproxen and low dose rofecoxib vs. naproxen the entire 95% CIs were above the pre-assigned non-inferiority margin of 0.5. However, as mentioned earlier the Division considered the non-inferiority margin of 0.5 as too wide. In ITT population the lower limits of the 95% CIs were 0.76 for higher dose rofecoxib vs. naproxen and 0.61 for lower dose rofecoxib vs. naproxen. Therefore, for non-inferiority margin greater than 0.61 the lower dose of rofecoxib would fail to establish non-inferiority to Naproxen. The medical officer's preference of non-inferiority margin is 0.75 (see medical officer's review). Also, in many subgroups the low dose group did not establish non-inferiority even with a non-inferiority margin of 0.5.

In light of the above discussion and in consultation with the medical reviewer, this reviewer concludes that rofecoxib dose of 0.3 mg/kg/day did not show non-inferiority in treatment effect measured in JRA 30 when compared to naproxen.

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

The clinical adverse experience profile is summarized by assigned treatment groups in Table 8 in Appendix 1. Clinical adverse experiences were reported by 196 (63.2%) of 310 patients in the combined base study. One or more clinical adverse experiences occurred in 72 (66.1%), 61 (61.0%),

and 63 (62.4%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen groups, respectively. Drug-related (determined by the investigator to be possibly, probably, or definitely drug related) clinical adverse experiences occurred in 21 (19.3%), 22 (22.0%), and 28 (27.7%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen groups, respectively. Serious adverse experiences occurred in 1 (0.9%), 2 (2.0%), and 1 (1.0%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen groups, respectively. Of these patients, 1 (lower-dose rofecoxib treatment group) discontinued the study. None of the serious adverse experiences was determined to be drug related. No patients died during the study. In total 3 (2.8%), 0 (0.0%), and 2 (2.0%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen groups, respectively, discontinued study drug due to clinical adverse experiences. Of the patients who discontinued study drug due to adverse experiences, 2 (1.8%), 0 (0.0%), and 2 (2.0%) in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen groups, respectively discontinued due to drug-related adverse experiences. No patient was discontinued due to a serious drug-related adverse experience. The three most commonly reported adverse experiences were abdominal pain, upper abdominal pain, and headache. Drug-related adverse experiences occurred most frequently in the gastrointestinal system. Eighteen (16.5%), 18 (18.0%), and 19 (18.8%), of the patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen treatment groups experienced drug-related digestive system adverse experiences. The drug-related adverse experiences most frequently seen in this system were abdominal pain and upper abdominal pain. Drug-related adverse experiences in the nervous system occurred in 3 (2.8%), 3 (3.0%), and 9 (8.9%) patients in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen treatment groups, respectively. The excess of drug-related adverse experiences in the naproxen group was mostly attributable to the incidence of headache which was higher in the naproxen group with 6 (5.9%) of the patients reporting this adverse experience. Three (2.8%) and 1 (1.0%) of the patients in the lower-dose rofecoxib, and higher dose rofecoxib treatment groups, respectively, had drug-related adverse experiences of headache. The adverse experience profile in 2 to 11 year olds and 12 to 17 year olds was similar to the overall population.

Five patients discontinued due to clinical adverse experiences: 3 (3.0%) in the lower-dose rofecoxib treatment group and 2 (2.0%) in the naproxen treatment group. Of the 3 patients in the lower-dose rofecoxib treatment group, 2 patients discontinued due to clinical adverse experiences of abdominal pain, which were determined by the investigator to be study-drug related. The third patient discontinued due to worsening of juvenile rheumatoid arthritis, which was determined by the investigator to be non-study-drug related. Of the 2 patients in the naproxen treatment group, AN 391 discontinued due to a clinical adverse experience of migraine, which was determined by the investigator to be related to study drug. AN 475 discontinued due to a clinical adverse experience of hematochezia, which the investigator determined to be related to study drug (Table 49).

Nonfatal serious clinical adverse experiences occurred in 4 (1.3%) of 310 patients. The incidence of serious clinical adverse experiences was 1, 2, and 1 in the lower-dose rofecoxib, higher dose rofecoxib, and naproxen treatment groups, respectively. None of the serious adverse experiences was determined by the investigator to be drug related. There were no patient deaths in this study.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed the following subgroup analysis: 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 (< median years, ≥median years), Erythrocyte sedimentation rate (0 to 20, ≥20), Baseline methotrexate user (Yes, No), Baseline low-dose corticosteroid user (Yes, No), Baseline disease-modifying anti-rheumatic drugs user (Yes, No), Prior naproxen user (Yes, No), and Prior. NSAID users.

The results showed that the therapeutic effect in 2 to 11 year old JRA patients and in 12 to 17 year old JRA patients were similar to those in the combined population of 2 to 17 year old JRA patients except for the following:

- Similar to results in the entire 2 to 17 year old population, for 12 to 17- year olds, the proportion of patients meeting the JRA 30 criteria in the higher dose rofecoxib group was non-inferior to that in the naproxen treatment group. In the lower dose rofecoxib treatment group fewer 12 to 17 year olds responded to treatment, as defined by the JRA 30 criteria. The point estimate of the ratio of response rates, relative to naproxen was 0.63 and the lower limit of the 95% CI was 0.4, less than the pre-specified margin of 0.5.
- For 2 to 11 year olds, the rofecoxib treatment groups had greater improvement from baseline in parent/patient's global assessment of pain than the naproxen treatment group.
- For 12 to 17 year olds, the lower-dose rofecoxib treatment group had a smaller treatment effect than the naproxen treatment group in the number of joints with active arthritis.

In the following subgroups low-dose did not show non-inferiority compared to Naproxen i.e. lower 95% CI were not greater than 0.5: Poly articular, 12 to 17 year, Male, Tanner Stage 2, 3, 4, and 5, Multi-racial, Duration of JRA < 3 years, Erythrocyte Sedimentation Rate 0 to 20, Methotrexate user, Corticosteroid user, DMARD user, Naproxen non-user, and NSAID non-users. In the following subgroups high-dose did not show non-inferiority compared to Naproxen i.e. lower 95% CI were not greater than 0.5: Male, Tanner Stage 3 and 4, Corticosteroid user, and NSAID non-users.

The sponsor also evaluated the treatment effect among patients who completed the 12 week base study. The results of this sub group analysis support the findings of the primary analysis. The analysis of JRA 30 among patients who either completed the base study or discontinued due to lack of efficacy with patients discontinued as non-responders also showed similar results and support the findings of the primary analysis.

4.1 REVIEWER'S ANALYSIS OF SUBGROUP POPULATION:

On the advice of the medical officer this reviewer perform subgroup analysis based on the age and bodyweight subgroups. The medical officer selected these subgroups based on some clinical importance. Tables 9 and 10 show this reviewer's analysis results for age and bodyweight subgroups.

Results of this reviewer's analysis showed decreasing treatment effect with increasing age and increasing bodyweight.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this submission the sponsor included report of a Phase 3 study, namely Study #P134 (Protocol134/135). This was a 12 week, double-blind, double dummy; active comparator controlled study in 2 to 17 years old juvenile rheumatoid arthritis patients. In each age group, patients were allocated to receive 1 of the 3 treatments: (1) lower dose rofecoxib, 0.3 mg/kg/day for 2 to 11 year old patients (not to exceed 12.5 mg/day), or 12.5 mg daily for 12 to 17 year old patients; (2) higher dose rofecoxib, 0.6 mg/kg/day for 2 to 11 year old patients (not to exceed 25 mg/day), or 25 mg daily for 12 to 17 year old patients; (3) naproxen, targeted to 15 mg/kg/day. The 2 to 11 year old patients received suspension formulations, and the 12 to 17 year old patients received tablets. The primary objectives of this study were to examine the therapeutic effects and safety of two doses of rofecoxib and to show the non-inferiority of rofecoxib compared to naproxen.

The primary efficacy endpoint was proportion of patients in the ITT population meeting the JRA 30 criteria. The non-inferiority is claimed if the 95% confidence interval on the relative risk (ratio of percent of patients meeting the JRA 30 criteria) of rofecoxib vs. naproxen was entirely above 0.5. However, the Division considered the non-inferiority margin of 0.5 as too wide.

Since there was only one study, the collective evidence is based on only one study. The results showed that in ITT population the lower limits of the 95% CIs were 0.76 for higher dose rofecoxib vs. naproxen and 0.61 for lower dose rofecoxib vs. naproxen. Therefore, 0.61 would be the largest non-inferiority margin for both doses of rofecoxib would be non-inferior to naproxen.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The primary efficacy endpoint was proportion of patients in the ITT population meeting the JRA 30 criteria. The non-inferiority is claimed if the 95% confidence interval on the relative risk (ratio of percent of patients meeting the JRA 30 criteria) of rofecoxib vs. naproxen was entirely above 0.5.

The results from both ITT and completers analyses showed that for both higher dose of rofecoxib vs. naproxen, and lower dose vs. naproxen the 95% CIs on risk ratios were above 0.5.

However, the Division considered the non-inferiority margin of 0.5 as too wide. In ITT population the lower limits of the 95% CIs were 0.76 for higher dose rofecoxib vs. naproxen and 0.61 for lower dose rofecoxib vs. naproxen. Therefore, for non-inferiority margin greater than 0.61 the lower dose of rofecoxib would fail to establish non-inferiority to Naproxen. The medical officer's preference of non-inferiority margin is 0.75 (see medical officer's review). Also, in many subgroups the low dose group did not establish non-inferiority even with a non-inferiority margin of 0.5.

In light of the above discussion and in consultation with the medical reviewer, this reviewer concludes that rofecoxib dose of 0.3 mg/kg/day did not show non-inferiority in treatment effect measured in JRA 30 when compared to naproxen.

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6 APPENDIX-1

6.1 TABLE 1: PATIENT DISPOSITION

Overall Disposition of Patients

Time Frame	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)
Treatment and Post-study	n=109	n=100	n=101
patient completed	26	18	14
patient discontinued	10	5	10
clinical AE	3	0	3
laboratory AE	3	1	0
lack efficacy	3	4	4
lost to follow-up	0	0	3
patient discontinued for other	1	0	0
patient extended	73	77	77

Although patients are counted only once within a Time Frame, patients may be counted in more than one Time Frame.

Source Table 4.31.7 of sponsor's analysis

6.2 TABLE 2: BASELINE DEMOGRAPHIC CHARACTERISTICS

	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								
1 and Under	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
2 to 4	15	(13.8)	22	(22.0)	9	(8.9)	46	(14.8)
5 to 11	50	(45.9)	38	(38.0)	47	(46.5)	135	(43.5)
12 to 17	44	(40.4)	40	(40.0)	45	(44.6)	129	(41.6)
Over 12 to 17	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
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		2-17		2-16		2-17		2-17
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)

Source Table 4.31.10 of sponsor's analysis

6.3 TABLE 3: ENDPOINTS AND THEIR STATISTICAL ANALYSES

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.
Data Source: [3.4]
Source Table 10 of sponsor's analysis

6.4 TABLE 4: SPONSOR'S ANALYSES OF PRIMARY EFFICACY VARIABLES

(Modified Intention-to-Treat Approach)

JRA 30 Responder During the 12 week Base Study: Regardless of Completion Status (Primary)†

Treatment	Frequency (%)	
Lower-Dose Rofecoxib	49 /106	(46.2)
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)
Lower Dose Rofecoxib vs. Naproxen	0.81 (0.61, 1.07)	-10.7 (-23.9, 2.5)
Higher Dose vs. Lower Dose Rofecoxib	1.21 (0.92, 1.60)	9.6 (-3.7, 22.8)

JRA 30 Responder and Completer (Secondary)

Treatment	Frequency (%)	
Lower-Dose Rofecoxib	48 /106	(45.3)
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)
Lower Dose Rofecoxib vs. Naproxen	0.81 (0.61, 1.09)	-10.0 (-23.1, 3.1)
Higher Dose vs. Lower Dose Rofecoxib	1.24 (0.94, 1.64)	10.5 (-2.7, 23.7)

† 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, 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.

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. AN 10 in the naproxen treatment group discontinued and his JRA 30 response criteria could not be evaluated because his efficacy measurements were not collected during on-treatment period. This patient was counted as a non-responder in the secondary analysis because the patient had discontinued. However, since his JRA 30 criteria could not be evaluated, this patient could not be included in the primary analysis.

JRA = Juvenile Rheumatoid Arthritis.

Source Table 21 of sponsor's analysis

6.5 TABLE 5: SPONSOR'S ANALYSES OF PRIMARY EFFICACY VARIABLES

(Per-Protocol)

JRA 30 Responder: Regardless of Completion Status (Primary)†

Treatment	Frequency (%)	
Lower-Dose Rofecoxib	53 /97	(54.6)
Higher dose Rofecoxib	52 /90	(57.8)
Naproxen	48 /87	(55.2)

Between-Group Comparison	Relative Risk‡ (95% CI)	Difference§ (95% CI)
Higher Dose Rofecoxib vs. Naproxen	1.04 (0.80, 1.35)	2.3 (-12.0, 16.6)
Lower Dose Rofecoxib vs. Naproxen	0.96 (0.73, 1.25)	-2.4 (-16.5, 11.6)
Higher Dose vs. Lower Dose Rofecoxib	1.10 (0.85, 1.42)	5.2 (-8.6, 18.9)

JRA 30 Responder and Completer (Secondary)

Treatment	Frequency (%)	
Lower-Dose Rofecoxib	49 /101	(48.5)
Higher dose Rofecoxib	51 /92	(55.4)
Naproxen	47 /94	(50.0)

Between-Group Comparison	Relative Risk‡ (95% CI)	Difference§ (95% CI)
Higher Dose Rofecoxib vs. Naproxen	1.08 (0.83, 1.42)	4.2 (-9.9, 18.2)
Lower Dose Rofecoxib vs. Naproxen	0.94 (0.70, 1.26)	-2.9 (-16.5, 10.7)
Higher Dose vs. Lower Dose Rofecoxib	1.17 (0.89, 1.53)	8.0 (-5.7, 21.6)

† 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, 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.

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. Four patients (ANs 237, 279, 552, and 636) on lower-dose Rofecoxib, 2 patients (ANs 4 and 128) on the higher dose
Rofecoxib, and 7 patients (ANs 1, 10, 116, 293, 312, 391, and 475) on naproxen discontinued and their JRA 30
response criteria could not be evaluated because insufficient efficacy measurements were collected. These patients
were counted as non-responders in the secondary analysis because they had discontinued. However, since these
patients' JRA 30 criteria could not be evaluated, they could not be included in the primary analysis.
JRA = Juvenile Rheumatoid Arthritis.

Data Source: [4.3]

6.6 TABLE 6: PARENT/PATIENT'S ASSESSMENT OF OVERALL WELL-BEING

(Pop: Modified Intent to Treat)

Treatment	Frequency†	(%)
Lower-Dose Rofecoxib	81 /109	(74.3)
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)
Lower-Dose Rofecoxib vs. Naproxen	1.01 (0.86, 1.20)	1.0 (-10.9, 12.8)
Higher dose vs. Lower-Dose Rofecoxib	1.03 (0.87, 1.21)	2.2 (-9.5, 14.0)

† 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.

Data Source: [4.3]

6.7 TABLE 7: PATIENT'S GLOBAL ASSESSMENT OF PAIN

(Modified Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Lower-Dose Rofecoxib	109	42.08	29.01	-13.07	20.80	-12.50	(-15.98, -9.02)
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
Lower-Dose Rofecoxib vs. Naproxen	-4.07	(-8.95, 0.80)	0.101
Higher dose vs. Lower-Dose Rofecoxib	-0.62	(-5.48, 4.25)	0.803

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.

Data Source: [4.3]

6.8 TABLE 8: SPONSOR'S ANALYSES OF SAFETY DATA

	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.

Data Source: [4.1; 4.20; 4.32]

6.9 TABLE 9: SUBGROUP ANALYSIS OF JRA 30 RESPONDER RATES BY AGE

Assuming missing value as missing			
Dose Groups	Age Sub-Group (Years)	Number of Patients	Relative Risk (95% CI)
Higher Dose Rofecoxib vs. Naproxen	All Age Group	54/99, 54/98	0.99 (0.76, 1.28)
Higher Dose Rofecoxib vs. Naproxen	2≤ Age ≤5	15/24, 6/11	1.15 (0.64, 2.87)
Higher Dose Rofecoxib vs. Naproxen	6≤ Age ≤11	18/35, 22/42	0.98 (0.62, 1.53)
Higher Dose Rofecoxib vs. Naproxen	12≤ Age ≤17	21/40, 26/45	0.91 (0.61, 1.34)
Lower Dose Rofecoxib vs. Naproxen	All Age Group	49/106,54/98	0.84 (0.63, 1.10)
Lower Dose Rofecoxib vs. Naproxen	2≤ Age ≤5	12/23, 6/11	0.96 (0.48, 2.49)
Lower Dose Rofecoxib vs. Naproxen	6≤ Age ≤11	20/40, 22/42	0.95 (0.61, 1.47)
Lower Dose Rofecoxib vs. Naproxen	12≤ Age ≤17	17/43, 26/45	0.68 (0.42 ,1.07)
Assuming missing value as failure			
Dose Groups	Age Sub-Group (Years)		Relative Risk (95% CI)
Higher Dose Rofecoxib vs. Naproxen	All Age Group	54/100, 54/101	1.01 (0.78, 1.31)
Higher Dose Rofecoxib vs. Naproxen	2≤ Age ≤5	15/25, 6/12	1.20 (0.65, 3.06)
Higher Dose Rofecoxib vs. Naproxen	6≤ Age ≤11	18/35, 22/44	1.03 (0.65, 1.61)
Higher Dose Rofecoxib vs. Naproxen	12≤ Age ≤17	21/40, 26/45	0.91 (0.60, 1.35)
Lower Dose Rofecoxib vs. Naproxen	All Age Group	49/109, 54/101	0.84 (0.63, 1.11)
Lower Dose Rofecoxib vs. Naproxen	2≤ Age ≤5	12/24, 6/12	1.00 (0.49, 2.62)
Lower Dose Rofecoxib vs. Naproxen	6≤ Age ≤11	20/41, 22/44	0.98 (0.62, 1.52)
Lower Dose Rofecoxib vs. Naproxen	12≤ Age ≤17	17/44, 26/45	0.67 (0.41, 1.05)

Reviewer's table

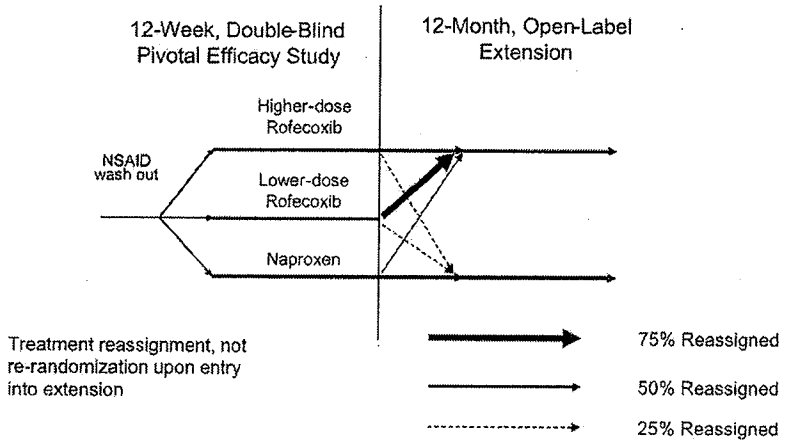
6.10 TABLE 10: SUBGROUP ANALYSIS OF JRA 30 RESPONDER RATES BY BODYWEIGHT

Dose Groups	Bodyweight Sub-Group (Kg)	Age (Years) n, Mean (Min, Max)	Number of Patients	Relative Risk (95% CI)
Assuming missing value as missing				
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)
Lower Dose Rofecoxib vs. Naproxen	All Bodyweight Group	204, 10.25 (2.00, 17.00)	49/106, 54/98	0.84 (0.63, 1.10)
Lower Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	37, 4.24 (2.00, 7.00)	11/21, 9/16	0.93 (0.49, 1.92)
Lower Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	83, 9.39 (4.00, 17.00)	21/46, 19/37	0.89 (0.56, 1.43)
Lower Dose Rofecoxib vs. Naproxen	Bodyweight>= 40	84, 13.75 (9.00, 17.00)	17/39, 26/45	0.75 (0.47, 1.17)
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)
Lower Dose Rofecoxib vs. Naproxen	All Bodyweight Group	210, 10.18 (2.00, 17.00)	49/109, 54/101	0.84 (0.63, 1.11)
Lower Dose Rofecoxib vs. Naproxen	10≤ Bodyweight <20	39, 4.20 (2.00, 7.00)	11/22, 9/17	0.94 (0.49, 1.96)
Lower Dose Rofecoxib vs. Naproxen	20≤ Bodyweight <40	86, 9.40 (4.00, 17.00)	21/48, 19/38	0.88 (0.55, 1.42)
Lower Dose Rofecoxib vs. Naproxen	Bodyweight >=40	85, 13.72 (9.00, 17.00)	17/39, 26/46	0.77 (0.48, 1.20)

Reviewer's table

Figure 1

Design of Pivotal Efficacy Study and Open-Label Extension



Source: Figure 2.7.3:1 of sponsor's submission

7 APPENDIX- 2

7.1 STATISTICAL ANALYSIS PLAN

I. DATA ANALYSIS

Statistical analysis of the data from this study will be the responsibility of the Clinical Biostatistics department of Merck Research Laboratories.

Hypotheses

The study hypotheses are as follows:

1. The proportion of patients that demonstrate improvement will be similar between rofecoxib and naproxen treatment groups. The primary endpoint for evaluating efficacy at the onset was the parent/patient's assessment of overall well being; however, as explained in the background section, prior to database unblinding, the primary endpoint was changed to JRA 30.

   Criteria for evaluation: The 95% CI for ratio of percent of patients demonstrating improvement from baseline (rofecoxib versus naproxen) will lie entirely above 0.5. A step-down procedure will be employed to compare each dose with naproxen. First, the CI for the higher rofecoxib dose versus naproxen will be compared to 0.5, and only if above 0.5 will the CI for the lower rofecoxib dose be compared to 0.5.

2. Administration of rofecoxib to children with JRA will be safe and well tolerated.

   Criteria for evaluation: 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.

Addressed objectives:

1. Mean change from baseline (averaged over all times of observation) will be compared between the 2 doses of rofecoxib in the 2- through 11 year old JRA patients, stratified by joint involvement (pauci versus poly).
2. Mean change from baseline (averaged over all times of observation) will be compared between the 2 doses of rofecoxib in the 12- through 17 year old JRA patients, stratified by joint involvement (pauci versus poly).
3. The safety and tolerability of rofecoxib in children with JRA will be assessed as described for the second hypothesis above.
4. The safety and efficacy profile of naproxen for treatment of JRA will be assessed and compared with that of rofecoxib as described for the hypotheses above.
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.

Variables/Time Points of Interest (Metric, Parameter)

The efficacy variables are (in priority order):

1. JRA 30
2. Parent/Patient's Assessment of Overall Well Being
3. Investigator's Global Assessment of Disease Activity
4. Functional Ability (CHAQ)
5. The Parent/Patient's Global Assessment of Pain
6. Number of Joints With Active Arthritis
7. Number of Joints With Limited Range of Motion
8. Proportion of patients discontinuing due to lack of efficacy
9. ESR

Initially, the parent/patient's assessment of overall well being was the primary endpoint; others were considered secondary. The primary endpoint has been replaced by JRA 30 after completion of the clinical portion of the trial, but prior to unblinding the database-refer to Background section for more detail. Parent/Patient's Assessment of Overall Well Being will also be assessed similarly to JRA 30, and inserted in the above priority list immediately after JRA 30, which will be first in the priority list. Note that power for JRA 30 is the same as for Parent/Patient's Assessment of Overall Well Being since both are binary endpoints; thus, the power section of this data analysis section is not revised; however, it is understood to apply to JRA 30.

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. In addition to the between-treatment group comparisons of proportions of patients with AEs and exceeding predefined limits of change in safety parameters as described above, means ±SE will be plotted over time for each laboratory and vital signs parameter.
For safety, the following list is of primary interest: discontinuations due to digestive adverse experiences or abdominal pain, clinical adverse experiences of hypertension and blood pressure increased, clinical adverse experiences of fluid retention and edema, laboratory adverse experiences of increased serum creatinine and increased serum hepatic transaminases (ALT and AST). Statistical significance testing for between-treatment group differences will be carried out for these endpoints. No significance testing will be carried out for other safety endpoints; their clinical relevance will be assessed on the basis of magnitude of effects using confidence intervals.

Approaches to Analyses

The primary analysis will be a modified intent-to-treat approach. All patients who take at least 1 dose of study drug and provide baseline and at least 1 postbaseline response will be included in the analysis of efficacy. Dropouts for various reasons are not unexpected. Dropouts will be included in the primary analysis based on their responses obtained up to and including the time of discontinuation. The primary analysis of clinical efficacy will be based on a stepdown procedure (high-dose rofecoxib versus naproxen first, and if the CI >0.5, followed by low-dose rofecoxib versus naproxen).

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 perprotocol

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.

Statistical Methods

The ratio of proportions of patients meeting the JRA30 criteria and the ratio of patients with improvement from baseline in parent/patient's assessment of overall well-being assessed using a Mantel-Haenszel ratio of rates. Discontinuations due to lack of efficacy, and for each primary safety endpoint will be assessed using Fisher's exact test since their expected rates are lower than those for the dichotomized efficacy endpoints. All individual efficacy variables except proportions of patients will be assessed by ANOVA (model to include terms for joint involvement stratum, age stratum, baseline covariate, and treatment group). The interactions with treatment will be evaluated; if significant at the 0.05 level, their qualitative nature will be assessed using exploratory data analytic techniques. Least-squares mean differences between rofecoxib doses and naproxen will be compared via t-tests derived from the ANOVA. Assumptions of normality and homogeneity will be assessed by the Shapiro-Wilk statistic and Levene's test.

Multiplicity

No adjustment for multiplicity is needed because there is only 1 primary hypothesis for efficacy. Making no multiplicity adjustment for safety is conservative, and enhances power to find untoward effects if present. Hence, no multiplicity adjustment will be made.

Sample Size and Power Calculations

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.

Interim Analyses

The sample size may be adjusted during the trial based on blinded assessment of the overall study response rate. This is because the variance of the rate ratio depends on the rates. Since this type of adjustment is made blinded to treatment, and there will be only 1 final unblinded analysis, there will be no adjustment to the alpha level of 0.05. There will be no unblinded interim analysis.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDAs	21-042/(SE5-026) & 21-052/(SE5-019)
Submission Dates	12/5/2003; 2/17/2004; 4/22/2004; 4/29/2004; 5/7/2004
Brand Name	VIOXX™ 12.5 mg and 25 mg Tablets VIOXX™ 12.5 mg/5 mL and 25 mg/5 mL Oral Suspension
Generic Name	Rofecoxib
Reviewer	Lei Zhang, Ph.D.
PM Reviewer	Jenny J. Zheng, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND Division	DAAODP (HFD-550)
Sponsor	Merck & Co., Inc.
Relevant IND	46,894
Submission Type	SE5 (Different/New Population)
	Labeling Changes with New Indications in Pediatric Populations
	Pediatric Exclusivity Determination Requested

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 2
1.1 Recommendations 3
1.2 Phase 4 Commitments 3
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings 3
1.4 Pediatric Decision Tree 5
1.5 Written Request (WR) Fulfillment-CPB Related 6
2 QUESTION BASED REVIEW 7
2.1 General Attributes 7
2.2 General Clinical Pharmacology 9
2.3 Intrinsic Factors 12
2.4 Extrinsic Factors 15
2.5 General Biopharmaceutics 16
2.6 Analytical 16
3 DETAILED LABELING RECOMMENDATIONS 17
4 APPENDICES 20
4.1 Proposed Package Inserts from the Sponsor 20
4.2 Individual Study Review 40
4.2.1 Adult RA Patients (Protocol 228) 40
4.2.2 JRA Patients (12-17 yrs) (Protocol 105, Part I) 46
4.2.3 JRA Patients (2-11 yrs) (Study 109c) 53
4.2.4 JRA Patients (2-5 yrs) (Study 109c2) 62
4.3 Pharmacometric (PM) Review 70

1 EXECUTIVE SUMMARY

Vioxx (Rofecoxib), an orally active cyclooxygenase-2 (COX-2) inhibitor, was approved on May 20, 1999 for the relief of the signs and symptoms of osteoarthritis (OA), for the management of acute pain in adults, and for the treatment of primary dysmenorrhea. A supplement NDA was approved on April 11, 2002 for the relief of the signs and symptoms of rheumatoid arthritis (RA) in adults. In March 2004, it was approved for the acute treatment of migraine attacks with or without aura in adults (NDA 21-647).

The Sponsor submitted this supplemental application (for both NDA 21-042 and NDA 21-052) to fulfill the requirements listed in FDA's Written Request (WR) issued on December 6, 2001 and May 14, 2003 amendment. The Sponsor is seeking pediatric exclusivity, and labeling changes that include a new indication in the treatment of signs and symptoms of juvenile rheumatoid arthritis (JRA) for Vioxx. Relatively few nonsteriodal anti-inflammatory drugs (NSAIDs), no COX-2 inhibitor, have been prospectively studied and approved for use in pediatric patients compared with adult arthritis patients. The addition of rofecoxib to the therapeutic armamentarium for JRA could represent a treatment advance.

According to the Pediatric Decision Tree (Section 1.4), the Sponsor needs to conduct both PK studies and safety and efficacy trials because we could not assume that pediatric JRA patients are similar to adult RA patients with regard to disease progression. Therefore, the Sponsor conducted both PK and safety and efficacy studies. This application consists of four PK studies (three in JRA patients aged 2-17 yrs and one in adult RA patients) and one clinical efficacy/safety study in JRA patients aged 2-17 yrs (with a 52-week open-label extension). The Sponsor has fulfilled the requirements listed in WR and FDA granted the pediatric exclusivity on February 18, 2004.

To guide dose selection for JRA patients, steady-state pharmacokinetics of rofecoxib was characterized in patients (aged 2-17 years old) with pauci (oligo)- or poly-articular course JRA. In addition, steady-state PK was characterized in adult RA patients for comparison. As part of the WR, changes in drug oral clearance (CL/F) were pre-defined as the parameter of interest. Body weight, body surface area (BSA) and age were found to be the most important covariates that affect clearance of rofecoxib.

The Pediatric Written Request (PWR) called for a statistical comparison of the PK parameters of rofecoxib between pediatric JRA patients and adult RA patients. The Sponsor proposed dose recommendations of 0.6 mg/kg (up to 25 mg) for JRA patients 2-11 years old and 25 mg for adolescent JRA patients based on comparison of clearance and exposure of rofecoxib in JRA patients and healthy adults. The assumptions used were: 1) similar exposure-response in pediatrics and adult patients; 2) similar exposure in healthy adults and adult RA patients; and 3) dose-proportional exposure in the effective dose ranges in JRA and RA patients. In fact, clearance data from adult RA patients was 32% lower than that in healthy adults (63 mL/min vs. 92 mL/min), thus contradicting one of the Sponsor's *a priori* assumptions. Therefore, exposure (AUC_{0-24}) of rofecoxib under the proposed dose recommendations in JRA patients was lower than that in adult RA patients dosed at 25 mg dose with a Geometric Mean Ratio (GMR) of 0.77

(90% CI, 0.64, 0.93) but was comparable to AUC_{0-24} in healthy adults dosed at 25 mg dose with a GMR of 1.12 (90% CI, 0.98, 1.29).

Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the safety and efficacy of the recommended doses in JRA patients aged 2-17 years have been demonstrated in the pivotal 12-week, double-blind active-controlled study. Naproxen (7.5 mg/kg BID) was used as the active control. The response rates based on the endpoint of JRA Definition of Improvement ≥ 30% (JRA DOI 30) were 54.5% and 55.1% for rofecoxib and naproxen, respectively. Rofecoxib at the proposed doses was statistically non-inferior to naproxen. Efficacy of a lower dose rofecoxib, half of the proposed dose, was also studied and found to have a lower response rate, 46.2%. The lower rofecoxib dose failed to demonstrate non-inferiority to naproxen. There is no chronic safety experience at doses greater than those studied in this study. Hence, the proposed doses are acceptable although resulting in lower exposure in JRA patients compared to RA patients. (Please refer to Dr. Carolyn Yancey's review for details.)

There are 3 types of JRA: pauciarticular, polyarticular, and systemic. Because systemic course JRA patients were not included in either PK or safety/efficacy studies, the indication will be limited to the treatment of signs and symptoms of pauciarticular and polyarticular course JRA in pediatric patients aged 2 years and older who weigh more than 10 kg (22 lbs).

1.1 Recommendations

The Sponsor adequately characterized PK in JRA patients aged 2 years to 17 years old and evaluated effect of age and body weight on PK of Vioxx. The Office of Clinical Pharmacology and Biopharmaceutics has found this sNDA to be acceptable provided that satisfactory agreement is reached between the Sponsor and the Division regarding the language in the package insert (PI) and patient prescription information (PPI). Recommendations for consideration for the final labeling are included in the Labeling Section (Section 3) of the review.

1.2 Phase 4 Commitments

None. PK has been adequately characterized in both JRA patients (2-17 yrs) and adult RA patients, and no Phase 4 PK study is needed. However, population PK components may be added to additional clinical safety/efficacy trials to confirm exposure in patients either outside of the age/weight limits (e.g., < 10 kg) or to better refine dosage recommendations.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

This application consists of four PK studies: three in JRA patients aged 2-17 yrs and one in adult RA patients.

To guide dose selection for JRA patients, steady-state pharmacokinetics of rofecoxib was characterized in patients (aged 2-17 years old) with pauci- or poly-articular course JRA (Protocol 105 Part I, Protocol 109/110 Part I (or P109c) and Protocol 109/110 Part II (or P109c2)). In addition, steady-state PK was characterized in adult RA patients (Protocol 228) for comparison. As part of the WR, changes in drug oral clearance (CL/F) were pre-defined as the parameter of

interest as it is (ideally) dose independent and a fundamental parameter upon which both AUC and C_{max}, the more commonly used parameters, are dependent on.

Table 1.3.1. Rofecoxib Apparent Oral Clearance (CL/F, mean ± SD) in Pauciarticular and Polyarticular Course JRA Patients and Adults.

	JRA patients			Adults	
Group	2- to 5-year-old (N=21)	6- to 11-year-old (N=13)	12- to 17-year-old (N=11)	Adult RA Patients (N=12)	Healthy Adults* (N=26)
Dose	~0.32 mg/kg or 0.7 mg/kg	~0.32 mg/kg	12.5 or 25 mg	25 mg	25 mg
CL/F (mL/min)	37 ± 15	52 ± 13	87 ± 21	65 ± 20	96 ± 30

*Historical data from P042 and P043.

From analysis of the data, body weight, body surface area (BSA) and age were the most important covariates that affect clearance of rofecoxib. In general, clearance of rofecoxib increases with body weight and BSA. Clearance also increases with age between 2-11 years. In adolescents (12-17 years) and adults (<65 years) there is little age dependency on clearance. Clearance for adolescent JRA patients (12-17 yrs) is similar to clearance for healthy adults but higher than that for adult RA patients. Per the Vioxx labeling, clearance of rofecoxib declines with advancing age (>65 years). Examination of oral clearance by sex revealed no difference between genders, consistent with what have been found in adults. Differences in clearance by race were not explored because most subjects were classified as Caucasians or multiracial.

As noted earlier, in some respects the proper comparison to children with JRA would seem to be adults with RA. However, the available PK dataset for adult RA patients was limited (N=12) and does not fully reflect the demographics of the RA population in the pivotal clinical trials for Vioxx. Namely, patients weighed less in the PK trial than in the pivotal clinical trial (mean weight 62 kg vs. 73.1 kg) (Age and gender were similar between PK and clinical trials.). Because CL/F of rofecoxib increases with body weight, the oral clearance for these 12 PK patients may be somewhat lower than that in the RA population in the clinical trial and thus data obtained may overestimate the PK exposures (AUC) in the general RA population. However, 10 kg difference in body weight would not account for 30% difference in oral clearance between healthy adults and RA patients. The data from the healthy adults (mean weight 77.7 kg) were used for comparison to provide additional information on pharmacokinetic behavior of rofecoxib in adults.

The Sponsor proposed dose recommendations of [illegible] for JRA patients 2-11 years old and 25 mg for adolescent JRA patients based on comparison of clearance and exposure of rofecoxib in JRA patients and healthy adults because there was no PK data in adult RA patients available at that time. The assumptions used were: 1) similar exposure-response in pediatrics and adult patients; 2) similar exposure in healthy adults and adult RA patients; and 3) dose-proportional exposure in the effective dose ranges in JRA and RA patients. Later data from an adult RA patient PK trial suggested that clearance in RA patients was 32% lower than that in healthy adults (63 mL/min vs. 92 mL/min, geometric mean). Therefore, exposure (AUC_{0-24}) of

rofecoxib under these dose recommendations in JRA patients was lower than that in adult RA patients dosed at 25 mg dose but was comparable to AUC_{0-24} in healthy adults dosed at 25 mg dose (Table 1.3.2).

Table 1.3.2. Comparison of Dose-adjusted AUC(0-24hr)† (ng·hr/mL) for Pediatric Patients to Adults.

Age Group	N	Geometric Mean (ng·hr/mL)	GMR (JRAPatients/ Adults)	90% CI
JRA Patients	45	5102.2		
Adult RA Patients	12	6642.4	0.77	(0.64, 0.93)
Healthy Adults	26	4543.4	1.12	(0.98, 1.29)

† Dosing regimen of 0.6 mg/kg (2 to 11 years; capped at 25 mg) with the adolescents receiving a fixed 25 mg dose.

Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the safety and efficacy of the recommended doses in JRA patients aged 2-17 years have been demonstrated in the pivotal 12-week, double-blind active-controlled study (Protocol 134/135) with a 52-week open-label extension. The response rates based on the endpoint of JRA Definition of Improvement ≥ 30% (JRA DOI 30) were 54.5% and 55.1% for rofecoxib and naproxen (active comparator), respectively. The efficacy of rofecoxib at the proposed doses was statistically non-inferior to that of naproxen. There is no chronic safety experience at doses greater than those studied in this study. Hence, the proposed doses are acceptable.

1.4 Pediatric Decision Tree

Pediatric Study Decision Tree

Indication: Vioxx tablets and oral suspension are indicated for the relief of the signs and symptoms of rheumatoid arthritis (RA) in adults. In this application, the Sponsor is proposed for its use for the relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA).

1.5 Written Request (WR) Fulfillment-CPB Related

The following table lists summarized CPB-related WR requests and information submitted:

WR Items	Information Submitted
Steady State PK in JRA patients	Study Reports for Protocol 105 Part I, JRA 12-17 yrs Protocol 109/110 Part I: JRA 2-11 years Protocol 109/110 Part II: JRA 2-5 years
JRA patients (aged 2-17 yrs old) with at least one third of the patients approximately evenly distributed below the age of 6 years	Study Reports for Protocol 105 Part I, JRA 12-17 yrs Protocol 109/110 Part I: JRA 2-11 years Protocol 109/110 Part II: JRA 2-5 years
PK Data from a pre-specified RA database should be used for comparison to JRA group.	Study Reports for Protocol 228, adult RA
The effect of age on PK parameters will be evaluated.	Appendix. 2.7.2:1 Memo
The PK evaluation should be powered to detect a 30% change in mean apparent oral clearance (CL/F) and other relevant PK parameters compared to such values for adult RA patients.	Appendix. 2.7.2:2 Memo *Post-hoc* analysis. With 45 JRA patients and 12 adult RA patients, there would have been ~ 76.9% power to detect a 30% mean change (α=0.05, two-tailed, SD=0.2937) in CL/F.

Appropriate formulation for a pediatric population	Both tablet (in age 12-17) and oral suspension (in age 2-11) formulations were used in PK and clinical studies. Previous studies (P070) demonstrated that suspension and tablet formulations of rofecoxib are bioequivalent in adults under fasted conditions.

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

E. Dennis Bashaw, Pharm.D.
Clinical Pharmacology Team Leader
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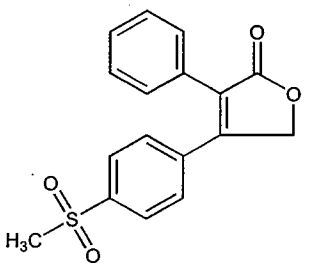
OCPB briefing (Required Office-Level) was held on May 24, 2004.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

VIOXX (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone. It has a molecular weight of 314.36. The following is its chemical structure:



There are two approved formulations of Vioxx: tablet (12.5, 25, 50 mg) and oral suspension (12.5 mg/5mL and 25 mg/5 mL).

2.1.2 What is the proposed mechanism of drug action? What are therapeutic indications of Vioxx?

Vioxx (Rofecoxib) is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, rofecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Vioxx has been previously approved for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthiris (RA), and for the management of acute pain in adults. It was also approved for the treatment of primary dysmenorrhea. In March 2004, it was approved for the acute treatment of migraine attacks with or without aura in adults (NDA 21-647).

In this application, the Sponsor is seeking the indication for the treatment of signs and symptoms of juvenile rheumatoid arthritis (JRA). JRA is a chronic inflammatory disease of childhood characterized by arthritis and, in some subjects, by extra-articular features (i.e. inflammatory mediated manifestations). JRA may occur in both males and females but is more predominant in females. It is classified into three types–polyarticular, pauciarticular, and systemic – distinguished either by symptoms at onset or, because the initial presentation does not necessarily predict subsequent disease manifestations, by disease course. Polyarticular JRA is the only subset that is similar to adult RA. Polyarticular JRA ($\geq$ 5 joints involved) affects approximately 30% of children with JRA. Pauci-articular JRA ($\leq$ 4 joints involved) and systemic JRA affect approximately 60% and 10% of children with JRA, respectively.

Because systemic course JRA patients were not included in either PK or safety/efficacy studies, the indication will be limited to the treatment of signs and symptoms of pauciarticular and polyarticular course JRA in pediatric patients.

2.1.3 What are the approved doses and route of administration in adults for RA and OA?

Vioxx is administered orally. The recommended dose for the treatment of signs and symptoms of RA in adult is 25 mg once daily. The maximum recommended daily dose is 25 mg.

For the treatment of signs and symptoms of osteoarthritis (OA) in adults, the recommended starting dose is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

2.1.4 What are the proposed doses for pediatric patients for JRA?

The Sponsor proposed a dose of 0.6 mg/kg to a maximum of 25 mg once daily for pediatric patients 2 to 11 years of age. To improve dosing accuracy for children weighing less than 40 kg, the use of

The porposed dose for adolescent patients 12 to 17 years of age is 25 mg once daily. The maximum recommended daily dose is 25 mg.

2.2 General Clinical Pharmacology

2.2.1 How does the steady state pharmacokinetics of rofecoxib in pediatric patients with JRA compared to PK of rofecoxib in adults (adult RA patients and healthy adults)?

Because different doses were used in the PK studies in pediatric patients and adults, only oral clearance (dose independent) were compared (Tables 2.2.1.1 and 2.2.1.2).

Two doses were used in JRA patients (2-5 years old) and adolescent JRA patients (12-17 years old). Oral clearance was the same for the two doses suggesting that exposure was dose proportional at the dose ranges studied. In adults, dose proportionality was demonstrated at the clinical dose range (10-50 mg). PK was nonlinear below the clinical dose range (<10 mg) in adults, and showed accelerated clearance.

Table 2.2.1.1. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients and Their Geometric Mean Ratios Versus Adult RA Patients.

Age Group	Dose	N	Cl/F Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (PN109/110 Part II)	~0.7 mg/kg	10	34.0	0.54	(0.42, 0.71)
2- to 5- years old (PN109/110 Part I)	~0.32 mg/kg	11	34.8	0.55	(0.42, 0.73)
6- to 11- years old (PN109/110 Part I)	~0.32 mg/kg	13	50.6	0.81	(0.67, 0.98)
12- to 17- years old (PN105)	12.5 or 25 mg	11	84.5	1.35	(1.11, 1.64)
RA Adults (PN228)	25 mg	12	62.7		

†Back-transformed from the log scale.

Table 2.2.1.2. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients and Their Geometric Mean Ratios Versus Healthy Adults.

Age Group	Dose	N	Cl/F Adjusted Mean†	GMR†	90% CI†
Combined 2- to 5- years old	~0.32 or ~0.7 mg/kg	21	34.4	0.37	(0.31, 0.44)
2- to 5- years old	~0.7 mg/kg	10	34.0	0.37	(0.30, 0.45)
2- to 5- years old	~0.32 mg/kg	11	34.8	0.38	(0.30, 0.47)
6- to 11- years old	~0.32 mg/kg	13	50.6	0.55	(0.47, 0.64)
12- to 17- years old	12.5 or 25 mg	11	84.5	0.91	(0.77, 1.08)
Healthy Adults	25 mg	26	92.4		

†Back-transformed from the log scale.

2.2.2 Were PK studies in JRA patients powered to detect a 30% mean change in apparent oral clearance (CL/F) between JRA patients and adults?

No power estimates for CL/F were calculated when the JRA studies were originally designed. Instead these protocols were designed to show comparable exposures (based on AUC) and were adequately powered on this endpoint (refer to Protocols 105 and 109/110: Parts I and II). No PK data were available for adult RA patients at the time that the PK studies in JRA patients were

being designed. To fulfill the requirement in WR, the sponsor conducted a *post-hoc* analysis to determine whether JRA PK studies were adequately powered to detect a 30% change in mean apparent oral clearance compared to adults.

With 45 JRA patients and 26 healthy adults, there would have been approximately 94.5% power to detect a 30% mean change (alpha=0.05, two-tailed, SD=0.2937) in CL/F. If based on healthy adult data, the JRA studies were adequately powered (> 80%).

With 45 JRA patients and 12 adult RA patients, there would have been approximately 76.9% power to detect a 30% mean change (alpha=0.05, two-tailed, SD=0.2937) in CL/F. If based on adult RA data, the JRA studies were slightly under-powered (< 80%).

2.2.3 How were the doses chosen for the pediatric clinical trials?

Based on comparison of clearance of rofecoxib in JRA patients and healthy adults, the Sponsor proposed that doses of 0.6 mg/kg (up to 25 mg) for JRA patients 2-11 years old and 25 mg for adolescent JRA patients would generate comparable exposure in JRA patients to healthy adults (Table 2.2.3.1) and would be effective in JRA patients. They used assumptions that: 1) similar exposure-response in pediatrics and adult patients; 2) similar exposure in healthy adults and adult RA patients; and 3) dose-proportional exposure in the effective dose ranges in JRA and RA patients.

Table. 2.2.3.1. Comparison of Dose-adjusted AUC(0-24hr) (ng·hr/mL)† for Pediatric Patients to Healthy Adults Following Administration of Rofecoxib.

Age Group	N	Geometric Mean	Median	Min and Max	GMR	90% CI
2- to 5-year old	21	4851.2	4382.2	[redacted]	1.07	(0.91, 1.26)
6- to 11-year old	13	5700.1	5656.7		1.25	(1.04, 1.52)
12- to 17-year old	11	4928.4	5164.0		1.08	(0.89, 1.32)
Pediatric Patients	45	5102.2	5047.7		1.12	(0.98, 1.29)
Healthy Adults	26	4543.4	4712.2			

† Dosing regimen of 0.6 mg/kg (2 to 11 years; capped at 25 mg) with the adolescents receiving a fixed 25 mg dose.

However, later data from adult RA patients suggested that clearance in RA patients was 32% lower than that in healthy adults (63 mL/min vs. 92 mL/min, geometric mean), thus contradicting one of the Sponsor's *a priori* assumptions. Therefore, exposure (AUC_{0-24}) of rofecoxib under these dose recommendations in JRA patients was lower than that in adult RA patients dosed at 25 mg dose (Table 2.2.3.2).

Table 2.2.3.2. Comparison of Dose-adjusted AUC(0-24hr) (ng·hr/mL)† for Pediatric Patients to Adult RA Patients Following Administration of Rofecoxib.

Age Group	N	Geometric Mean	Median	Min and Max	GMR	90% CI
2- to 5-year old	21	4851.2	4382.2		0.73	(0.59, 0.90)
6- to 11-year old	13	5700.1	5656.7		0.86	(0.68, 1.08)
12- to 17-year old	11	4928.4	5164.0		0.74	(0.58, 0.94)
Pediatric Patients	45	5102.2	5047.7		0.77	(0.64, 0.93)
RA Adults	12	6642.4	6584.3			

† Dosing regimen of 0.6 mg/kg (2 to 11 years; capped at 25 mg) with the adolescents receiving a fixed 25 mg dose.

In the efficacy trial, the Sponsor tested two doses of rofecoxib: a lower and a higher dose. The higher dose would generate comparable AUC in healthy adults and lower dose was half of the higher dose (see Table below).

Lower-Dose Rofecoxib	0.3 mg/kg for JRA patients 2-11 years old and 12.5 mg for adolescent JRA patients
Higher-Dose Rofecoxib	0.6 mg/kg for JRA patients 2-11 years old and 25 mg for adolescent JRA patients

2.2.4 What was the clinical endpoint used to assess efficacy in clinical pharmacology studies?

The primary efficacy endpoint was the response rate assessed after 12 weeks of treatment based upon JRA Definition of Improvement ≥ 30% (JRA DOI 30) that is a composite of clinical, laboratory, and functional measures of JRA.

Table. 2.2.4.1. Response Rates Based on JRA DOI 30.

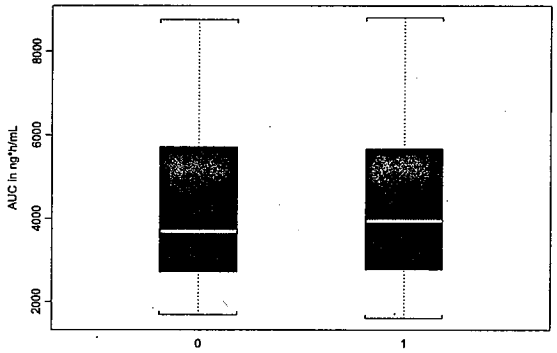
Dose	Response Rate	Rofecoxib/Naproxen (95% CI)
Lower-Dose Rofecoxib[a]	46.2%	0.84 (0.63, 1.10)
Higher-Dose Rofecoxib[b]	54.5%	0.99 (0.76, 1.28)
Naproxen (15 mg/kg/day)	55.1%	

[a] 0.3 mg/kg for JRA patients 2-11 years old and 12.5 mg for adolescent JRA patients
[b] 0.6 mg/kg for JRA patients 2-11 years old and 25 mg for adolescent JRA patients

The criterion for the non-inferiority was the lower limit of the 95% Confidence Interval (CI) for the ratio of response rate (rofecoxib/naproxen) to be ≥ 0.75. The results in Table 2.2.4.1 suggested that the efficacy of rofecoxib at the proposed doses was statistically non-inferior to that of naproxen. Lower dose rofecoxib, half of the proposed dose, had lower response rate and failed to demonstrate non-inferiority to naproxen.

2.2.5 What was the exposure-response relationship in pediatric patients with pauci- and poly-articular course JRA?

Based on the relationship between CL/F and bodyweight and the doses used, the exposures in the subjects recruited in efficacy study (both lower and higher dose rofecoxib) were calculated to examine whether the non-responders had lower exposures to rofecoxib. It appears that the mean exposure is similar between responders (N=103) and non-responders (N=102), indicating no apparent exposure response relationship was found (Figure 2.2.5.1).



0 represents non-responder and 1 represents responder

Figure 2.2.5.1. Predicted AUC of Responsoders vs. Non-Responder

Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the efficacy of the recommended doses in pauci- and poly-articular JRA patients aged 2-17 years have been demonstrated in the efficacy trial indicating that lower exposure in pediatric patients than adult RA patients had little clinical significance.

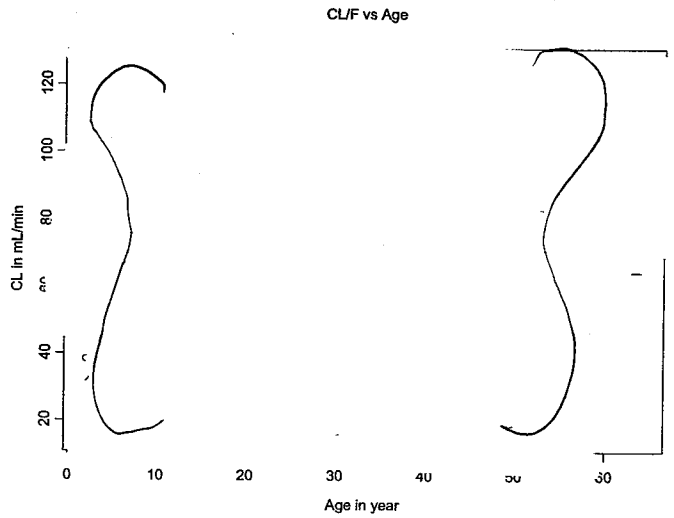
2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence PK of rofecoxib?

Body weight, body surface area (BSA) and age were found to be the most important covariates that affect clearance of rofecoxib. Please refer to Dr. Jenny J. Zheng's review (Section 4.3) for details.

Age:

The relationship between CL/F versus age was explored by the PM reviewer after excluding the PK data from healthy subjects. As shown in Figure 2.3.1.1, clearance increases with age between 2-11 years. In adolescents (12-17 years) and adults (< 65 years) there is little age dependency on clearance. Clearance for adolescent JRA patients (12-17 yrs) is higher than that for adult RA patients, and is similar to clearance for healthy adults (data not shown in the figure).

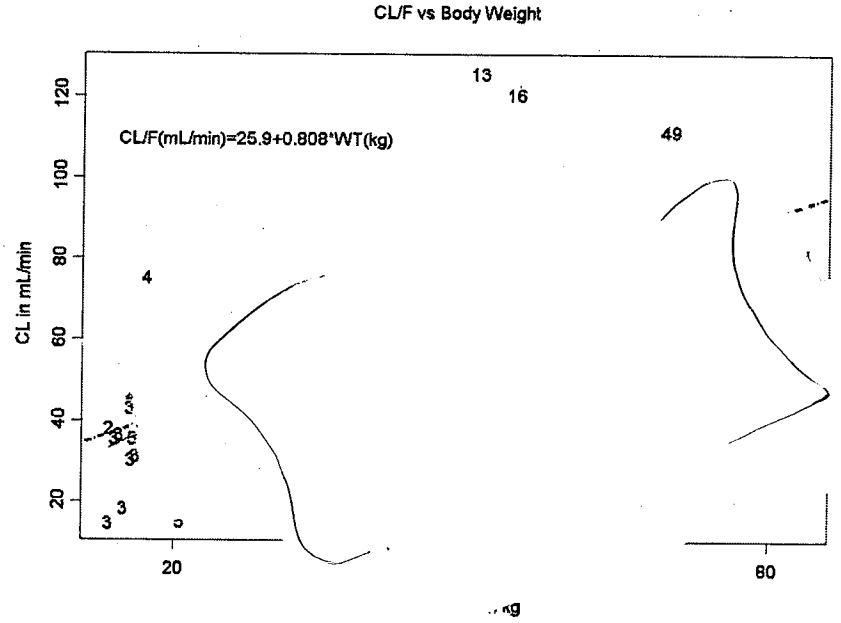


Dots represent the individual CL/F and line represents the lowess regression line

Figure 2.3.1.1. Relationship Between Oral Clearance (mL/min) and Age in JRA Patients and Adult RA Patients.

Body Weight:

Clearance of rofecoxib increases with body weight. It appears that there is a linear relationship but with a large y-intercept: CL/F (mL/min) = 26 + 0.808 * WT (in kg).



Numbers represent the individu.. s ages and the solid line represents the lowess regression line and the dash line represents the linear regression line

Figure 2.3.1.2. Relationship Between CL/F (mL/min) and Body Weight (kg) in JRA Patients and Adult RA Patients.

Body Surface Area (BSA):

Clearance of rofecoxib increases with BSA. It appears that there is a linear relationship with a y-intercept: CL/F (mL/min) = 14 + 36.1 * BSA (in m^2). BSA was calculated by the formula of DuBois and Dubois (Arch. Int. Med. 1916; 17:863-871): BSA = $0.007184 \cdot (\text{height}^{0.725}) \cdot (\text{weight}^{0.425})$, where height is in cm, weight is in kg and BSA is given in m^2.

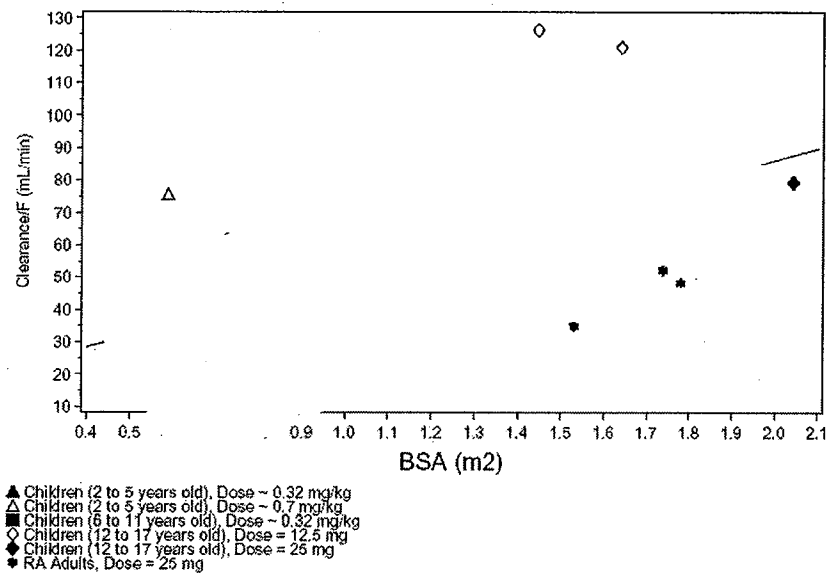


Figure 2.3.1.3. Relationship Between CL/F and Body Surface Area (m^2) in JRA Patients Aged 2 to 12 years, JRA patients Over 12, Healthy Adults Subjects and Adult RA Patients.

Gender:

Examination of oral clearance by sex revealed no difference between genders, consistent with what have been found in adults.

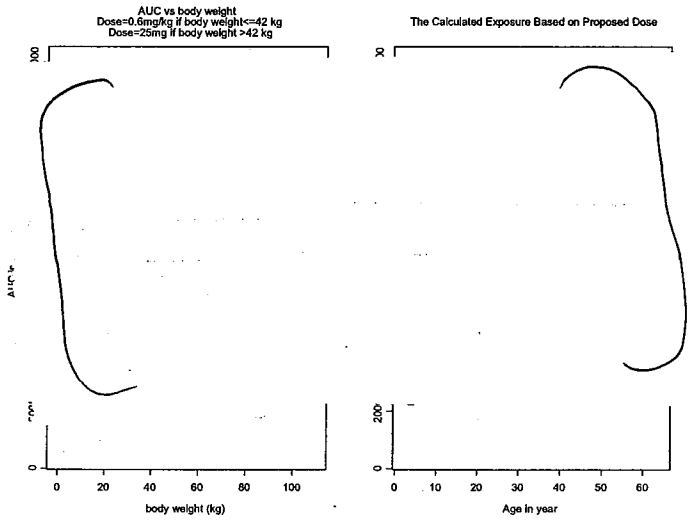
Race:

Differences in clearance by race were not explored because most subjects were classified as Caucasians or multiracial.

2.3.2 What is the dosing recommendation for the pediatric population based on the PK data?

The Sponsor proposed daily doses o [illegible] nd [illegible] Based on the relationship between body weight and clearance of rofecoxib, the Division would propose to base dose on body weight: 0.6 mg/kg for patients 10-42 kg and 25-mg doses for patients > 42 kg. Because there is an oral suspension formulation, dose recommendations based on body weight is appropriate. Because the actual clinical efficacy study stratified patients by age, age information could also be included in the dosage recommendation section.

Dose-adjusted exposure comparison of JRA patients at proposed doses and adults (RA patients and healthy subjects) at 25 mg are shown in Figure 2.3.2.1. As of note, the exposures shown in the left panel of the figure were calculated based on the relationship between CL/F and body weight (as proposed by the Division). The age effect on the CL/F was not considered. The exposures shown in the right panel of the figure were calculated based on the doses of 25 mg for subjects older than 12 years old and 0.6 mg/kg for the subjects less than 12 years old (as proposed by the Sponsor). As shown in the figure, the exposures in pediatric patients are slightly lower than the exposures in adult RA patients and the variability in pediatric patients is somewhat higher. However, the doses are supported by the clinical trial.



Left panel: Dots represent calculated individual AUC values for the subjects in the studies and the line represents the predicted mean exposure at different body weight according to formula: AUC=Dose*WT/(25.9+0.808*WT)

Right panel: Dots represent calculated individual AUC values for the subjects in the study based on proposed doses by the Sponsor and the line represents the lowess regression line.

Figure 2.3.2.1. Exposure comparison of JRA patients under Proposed Doses and Adults at 25 mg.

2.4 Extrinsic Factors

None that were pertinent to the pediatric population were identified.

2.5 General Biopharmaceutics

2.5.1 Is oral suspension formulation bioequivalent to tablet formulation?

Protocol 070 (previous data) demonstrated the bioequivalence of 12.5-mg rofecoxib tablets and 12.5-mg/5-mL rofecoxib oral suspension (and 25-mg rofecoxib tablets and 25-mg/5-mL rofecoxib oral suspension) in healthy adults under fasting conditions.

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage forms?

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when Vioxx Tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. Vioxx tablets can be administered without regard to timing of meals.

The food effect on the suspension formulation has not been studied.

2.6 Analytical

2.6.1 Were the analytical methods used to determine rofecoxib in biological fluids adequately validated?

Yes. Plasma samples for [redacted] were analyzed in accordance with protocol [redacted]. Plasma samples for [redacted] were analyzed in accordance with protocol [redacted] with minor modifications. Rofecoxib concentrations (both bound and free) were adequately measured in human plasma. The following table summarizes assay used for the PK studies in the submission:

Assay Method	HPLC using fluorescent detection after post-column photochemical conversion of analytes to fluorescent products
Analytical Site	[redacted]
Compound	Rofecoxib
Internal Standard	
Matrix	Plasma
Accuracy	[redacted]
Precision (CV%) *Interday*	[redacted]
Standard curve range	[redacted]
Sensitivity (LOQ)	[redacted]
Selectivity	Selective for rofecoxib and L-000755100. Control plasma samples did not contain detectable interferences at retention times of rofecoxib and L-000755100.
Stability	Stable in heparinized human plasma for at least 8 months at –20 °C (from original NDA 21-042/NDA 21-052 review)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-042 / S-026
21-052 / S-019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA **21-042, 21-052** SUPPL **026/019**

Trade Name **Vioxx™ Tablet and Suspension**

Generic Name **rofecoxib**

Applicant Name **Merck & Co, Inc.** HFD-**550**

Approval Date If Known **August 20, 2004**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES /✔/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✔/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7-years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /✓/ NO /___/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **21-042**

NDA# **21-052**

NDA# **21-647**

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✔/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✔/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✔/

(1) If the answer to 2(b) is "yes," do you personally

know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✔/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocols 134 and 135 (Protocol 134/135)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug

product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✔/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✔/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol 134/135

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or

its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		
INI	YES /✓/	NO /___/ Explain: _____
Investigation #2		
IND # _____	YES /___/	NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

Signature ***Barbara Gould*** Date ***30 July 2004***
Title:__ ***Project Manager***

Signature ***Brian E. Harvey*** Date
Acting Division Director

Form OGD-011347 Revised 05/10/2004

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

/s/

Brian Harvey
8/18/04 04:19:40 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 21-042 and 21-052 **Supplement Type (e.g. SE5): SE5** **Supplement Numbers: 026, and 019**

Stamp Date: December 05, 2003 **Action Date: August 20, 2004**

HFD-550 **Trade and generic names/dosage form: Vioxx™ (rofecoxib) Tablets, 12.5 mg, 25 mg and Suspension 12.5 mg/5 mL and 25 mg/5 mL**

Applicant: Merck & Co., Inc. **Therapeutic Class: Priority**

Indication(s) previously approved: Indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis in adults, management of acute pain in adults, treatment of primary dysmenorrhea, and for the acute treatment of migraine in adults

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years and older and who weigh 10 kg (22 lbs) or more.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☑ **No: Please check all that apply: ☑ Partial Waiver ____ Deferred ☑ Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr. 0 Tanner Stage____
Max____ kg < 10 mo.____ yr. < 2 Tanner Stage____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☑ **Too few children with disease to study**

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.** >2	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** <17	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 20-938**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Brian Harvey
8/18/04 02:52:57 PM

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-042

NAME OF APPLICANT / NDA HOLDER
Merck & Co., Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
VIOXX

ACTIVE INGREDIENT(S)	STRENGTH(S)
rofecoxib	12.5mg; 25mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by the FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,474,995	December 12, 1995	June 24, 2013

d. Name of Patent Owner		
Merck Frosst Canada & Co.	Address *(of Patent Owner)* 16711 Trans-Canada Hwy.	
	City/State Kirkland, Quebec, Canada	
	ZIP Code H9H 3L1	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3)and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		
	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

Computer generated form "Patent Submission with NDA" (Miscellaneous folder) Merck & Co., Inc. 8/27/2003

NDA 21-042 VIOXX®
(Rofecoxib Tablets)

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Rofecoxib
2. Dosage(s)	12.5mg, 25mg
3. Trade Name	VIOXX®
4. Dosage Form	Tablet
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	21-042
7. Approval Date	May 20, 1999
8. Exclusivity	Five (5) years NCE exclusivity from May 20, 1999 (May 20, 2004); Three (3) years from approval dates from pending supplements; and Six (6) months exclusivity* from the expiration dates of all patents listed below, as well as from the expiration dates of the data exclusivities for all pending or granted NDA and sNDA's. *Pursuant to Section 111 of the FDA Modernization Act and its subsequent amendment by the Best Pharmaceuticals for Children Act [Section 505A of the Federal Food, Drug and Cosmetic Act (21 U.S.C. Section 355a)], and the Guidance for Industry issued by FDA in June 1998 and revised in September 1999, pediatric exclusivity attaches to any exclusivity or patent protection that is, or will be, listed in the *Orange Book* for any drug product containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved NDA.
9. Applicable Patent Numbers	US Patent 5,479,995 Expires December 24, 2013 with pediatric market exclusivity US Patent 6,063,811 Expires November 6, 2017 with pediatric market exclusivity US Patent 6,239,173 Expires December 24, 2013 with pediatric market exclusivity

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

...completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-20
P.O. Box 4
West Point, PA 19486

Attn: Dennis M. Erb, Ph.D.

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 344-7597

3. PRODUCT NAME

VIOXX™ (Rofecoxib)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021042

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4644

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Dennis M. Erb	Executive Director, Regulatory Affairs	November 6, 2003

FORM FDA 3397 (1/03)

Rofecoxib – Juvenile Rheumatoid Arthritis
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Michele R. Flicker

Michele R. Flicker, M.D., Ph.D., FACP
Director
Regulatory Affairs

October 20, 2003
Date

TELECON MINUTES

Date: 3/1/01 **Time:** 3:30 pm

IND: ——

Drug: Vioxx (rofecoxib tablets and suspension)

Applicant: Merck & Co.

FDA Participants:

Dr. Jonca C. Bull	Acting Division Director
	Deputy Office Director
Dr. Maria Lourdes Villalba	Medical Officer
Ms. Sandra Folkendt	Project Manager

Merck Participants:

Dr. Robert Silverman	Senior Director, Regulatory Affairs
Dr. Alise Reicin	Clinical Research
Dr. James Bolognese	Clinical Biostatistics
Dr. Ken Truitt	Clinical Research
Dr. Michael Yellin	Clinical Research

Meeting Objectives:

The Division scheduled a teleconference with Merck to discuss their proposal for a pediatric written request, which was submitted on August 23, 2000.

FDA began the meeting by asking Merck if they planned a full juvenile rheumatoid arthritis (JRA) development plan since safety and efficacy in adult rheumatoid arthritis (RA) had not been established. Merck replied that they were unaware that establishing safety and efficacy in RA was a prerequisite.

Merck asked if the Division had specific comments on the protocol. The Division stated that the purpose of the teleconference at this time was to communicate the concern over lack of adult data and only one proposed pediatric study.

Concurrence:

Sandra N. Folkendt, Project Manager

Jonca C. Bull, M.D.
Acting Division Director

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

/s/

Jonca Bull
5/2/01 09:46:30 AM