Evaluation of the Comparative Efficacy and Tolerability of Rofecoxib and Naproxen in Children and Adolescents with Juvenile Rheumatoid Arthritis: A 12-Week Randomized Controlled Clinical Trial with a 52-Week Open-Label Extension

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ABSTRACT. ***Objective.*** To compare the safety and efficacy of rofecoxib* to naproxen for the treatment of juvenile rheumatoid arthritis (JRA).

Methods. This was a 12-week, multicenter, randomized, double-blind, double-dummy, active comparator-controlled, non-inferiority study with a prespecified 52-week open-label active comparator-controlled extension. Children (ages 2–11 yrs) and adolescents (ages 12–17 yrs) received lower-dose (LD)-rofecoxib [0.3 mg/kg/day up to 12.5 mg/day (base study only)]; or higher-dose (HD)-rofecoxib (0.6 mg/kg/day up to 25 mg/day) or naproxen 15 mg/kg/day as oral suspensions. Adolescents received daily rofecoxib (LD) 12.5 (base study only) or (HD) 25 mg, or naproxen 15 mg/kg/day (maximum 1000 mg/day) as tablets. The primary endpoint was the time-weighted average proportion of patients meeting the American College of Rheumatology Pediatric-30 (ACR Pedi 30) response criteria. A prespecified bound for the 95% confidence interval for the ratio of the percentage of ACR Pedi 30 responders was used to assess non-inferiority of treatment response between groups. Safety was assessed throughout the study.

Results. A total of 310 patients ages 2–17 years (181 ≤ age 11) were randomized to receive LD-rofecoxib (N = 109), HD-rofecoxib (N = 100), or naproxen (N = 101). The ACR Pedi 30 response rates following 12 weeks of treatment were 46.2%, 54.5%, and 55.1%, respectively. The relative rates of response compared to naproxen were 0.81 (95% CI 0.61, 1.07) and 0.98 (95% CI 0.76, 1.26) for LD- and HD-rofecoxib, respectively. Both rofecoxib doses were not inferior to naproxen. Patients (N = 227) entering the extension received HD-rofecoxib or naproxen with efficacy maintained during the extension. All treatments were generally well tolerated throughout the study.

Conclusion. Daily treatment of JRA patients with rofecoxib up to 12.5 or 25 mg was well tolerated, providing sustained clinical effectiveness comparable to naproxen 15 mg/kg. *On September 30, 2004, Merck & Co., Inc. announced the voluntary worldwide withdrawal of rofecoxib from the market.
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Key Indexing Terms:
ROFECOXIB TREATMENT JUVENILE RHEUMATOID ARTHRITIS DOUBLE BLIND TRIAL

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Juvenile rheumatoid arthritis (JRA) is one of the most common, chronic, painful inflammatory conditions in children[1,2] and encompasses several clinical subtypes (pauciarticular, polyarticular, and systemic onset). Treatment of JRA is guided by proper diagnosis, prognosis, and patient response to therapy. For certain JRA subtypes, particularly in patients with pauciarticular disease, nonsteroidal antiinflammatory drugs (NSAID) are often used as primary therapy to relieve joint pain and swelling. For the other subtypes, NSAID are frequently combined with disease modifying antirheumatic drugs (DMARD) or potent symptom modifying agents such as corticosteroids[3-5].

NSAID provide their analgesic and antiinflammatory clin-

ical benefits via inhibition of the cyclooxygenase-2 (COX-2) isoenzyme, a rate-limiting enzyme in the prostaglandin biosynthetic pathway. Concomitant inhibition of the COX-1 isoenzyme by traditional NSAID is associated with an elevated risk of gastrointestinal (GI) toxicity. This increased risk of GI toxicity is particularly evident in adult patients with RA exposed to continuous high doses of NSAID with intermittent corticosteroid use. In adults, the use of COX-2 selective inhibitors such as rofecoxib is associated with a significantly lower relative risk of clinically important upper and lower GI events compared to traditional NSAID[6-8]. Although the magnitude and consequences of NSAID-associated GI toxicity are less well defined in patients with JRA, they are nevertheless of concern[9-13]. GI symptoms such as dyspepsia and abdominal pain that are associated with traditional NSAID use may lead to poor compliance, discontinuation of study medications, or need to add additional gastroprotective medications for symptom relief[4,12,13]. Therefore, COX-2 selective inhibitors may offer an alternative to traditional NSAID for certain subsets of patients with JRA.

In adults, the COX-2 selective inhibitors represent a treatment option for RA[14,15]. Meloxicam, a partially selective COX-2 inhibitor, which also inhibits COX-1 at therapeutic concentrations[16], provides efficacy similar to naproxen 10–15 mg/kg/day for the treatment of juvenile rheumaoid arthritis when administered as an oral suspension[17]. Rofecoxib is a selective COX-2 inhibitor with a plasma half-life compatible with once-daily dosing. In addition, its availability as either an oral suspension or tablet provided dosage form flexibility in pediatric populations. The primary aim of our study was to compare a dose of rofecoxib approximating the 25 mg dose in adults, based on plasma concentrations over time, to naproxen 15 mg/kg/day in children and adolescents with JRA.

MATERIALS AND METHODS

Forty-one clinical centers in Australia, Europe, Asia, Central America, South America, and the United States participated in this study from December 4, 2000, to March 9, 2003, prior to rofecoxib being withdrawn from the worldwide market. The protocols and consent forms were approved by an Institutional Review Board or Ethics Review Committee for each study site. Each parent or guardian provided written informed consent prior to participation in the study. Where required, patients also provided written informed assent.

Patients. Children and study participants ages 2–17 yrs with pauci- (oligo) or polyarticular course JRA for ≥ 3 months meeting the American College of Rheumatology (ACR) Criteria for JRA were enrolled. Patients were stratified into 2 age cohorts consisting of children (age 2–11 yrs) and adolescents (age 12–17 yrs). Each patient was required to have a Parent/Patient's Assessment of Overall Well-being [100 mm visual analog scale (VAS)] of < 90 mm at the screening visit and > 10 mm, with at least one actively swollen joint, immediately prior to the first dose of study medication. Patients who completed the base study without a major protocol violation were permitted to enroll in the 52-week extension study.

Patients were excluded from the base study if they had active systemic JRA symptoms within 3 months of randomization or if they were not within the 5th to 95th percentile of weight for height. Patients who had hypersensitivity to aspirin and/or an NSAID, unstable antirheumatic medication regimens, or requiring alkylating agents, anticonvulsants, warfarin or rifampicin were also excluded. Female patients who had reached menarche were required to be in a nongravid state as determined by measurement of serum ß-HCG.

Study design. This was a 12-week (base study), multicenter, randomized, double-blind, double-dummy, active comparator-controlled non-inferiority study with a 52-week open-label extension to evaluate and compare the efficacy and safety of rofecoxib to naproxen for the treatment of JRA in patients 2–17 years old. Two clinical protocol numbers were assigned for the US (Protocol No. 134) and ex-US multinational (Protocol No. 135) portions of the trial for administrative reasons in order to satisfy regional regulatory requirements. Due to the chronic pain experienced by this pediatric patient population, which is often underestimated[2], a placebo-controlled study would have been unethical. Naproxen was chosen as the active-comparator traditional NSAID as it is an approved agent for the treatment of this condition.

In the base study, randomization to treatment groups in equal proportions was performed using a computer-generated allocation schedule. Treatment assignment was stratified based on joint involvement (pauci- or polyarticular course) and age group (2–11 or 12–17 yrs). Patients were assigned to one of 2 doses of rofecoxib or naproxen. Randomization for treatment reallocation at the start of the extension study was also done at this time; however, assignment to treatment groups was not balanced (Figure 1). Clinical assessments for efficacy and safety were performed at baseline and Weeks 2, 4, 8, 12, 25, 38, 51, and 64 on study therapy. A 14-day post-study followup visit was required for all patients following completion or discontinuation from the study.

The doses of rofecoxib selected for this study were based on its pharmacokinetic characteristics in patients with JRA[18-20] and its known effective dose range for the treatment of adult RA[21]. A dose of 0.6 mg/kg in children (age 2–11 yrs) or a dose of 25 mg in adolescents (age 12–17 yrs) yields similar plasma drug concentrations over time compared to rofecoxib 25 mg in adults. Naproxen at a dose of 15 mg/kg/day, in 2 divided doses, was used as the comparator. This dose is commonly prescribed for pediatric arthritis patients[22]. Children received LD-rofecoxib [0.3 mg/kg/day up to 12.5 mg/day (base study only) supplied as a 2.5 mg/ml oral suspension[20]]; or HD-rofecoxib (0.6 mg/kg/day up to 25 mg/day) supplied as 5.0 mg/ml oral suspension, or naproxen 15 mg/kg/day supplied as 25 mg/ml oral suspension. Adolescents received rofecoxib 12.5 or 25 mg qd or naproxen 15 mg/kg/day (maximum 1000 mg/day in 2 divided doses) as tablets. To maintain blinding to treatment assignment during the base study, each patient received 2 coded test products — active or identical-appearing placebo. Patients were instructed to take each test product once in the morning and one of the specific test products once in the evening [i.e., naproxen or naproxen placebo (in the base study)]. In the open-label extension study, patients received either HD-rofecoxib or naproxen as suspensions or tablets based on age group. Acetaminophen was allowed as rescue medication for pain. However, patients were instructed not to take acetaminophen within 24 hours of scheduled clinic visits. Compliance with study medication was assessed by measuring returned test product at each study visit.

Permitted and excluded medications. Continuation of treatment with conventional DMARD or biologics such as tumor necrosis factor-α inhibitors was allowed during the base study, provided doses were held constant beginning 6 weeks or 3 months prior to randomization, respectively. Intraarticular injections of corticosteroids were not allowed within 4 weeks prior to randomization and only one injection was allowed during the study. If a patient received an intraarticular injection of corticosteroid during the study period, that joint was rendered not evaluable for the purpose of joint counts. Oral corticosteroids (maximum equivalent of 0.2 mg/kg/day prednisone, not to exceed 10 mg/day) could be used as long as treatment was stable throughout the study beginning 4 weeks prior to randomization. In the open-label extension study, changes in DMARD therapy and intraarticular corticosteroids were permitted. Patients were instructed not to use other traditional NSAID or COX-2 selective inhibitors or salicylates during the study, and were required to discontinue previous NSAID therapy 72 hours prior to receiving the first dose of study medication. Although allowed in the protocol, no patient received low-dose aspirin for cardioprophylaxis.

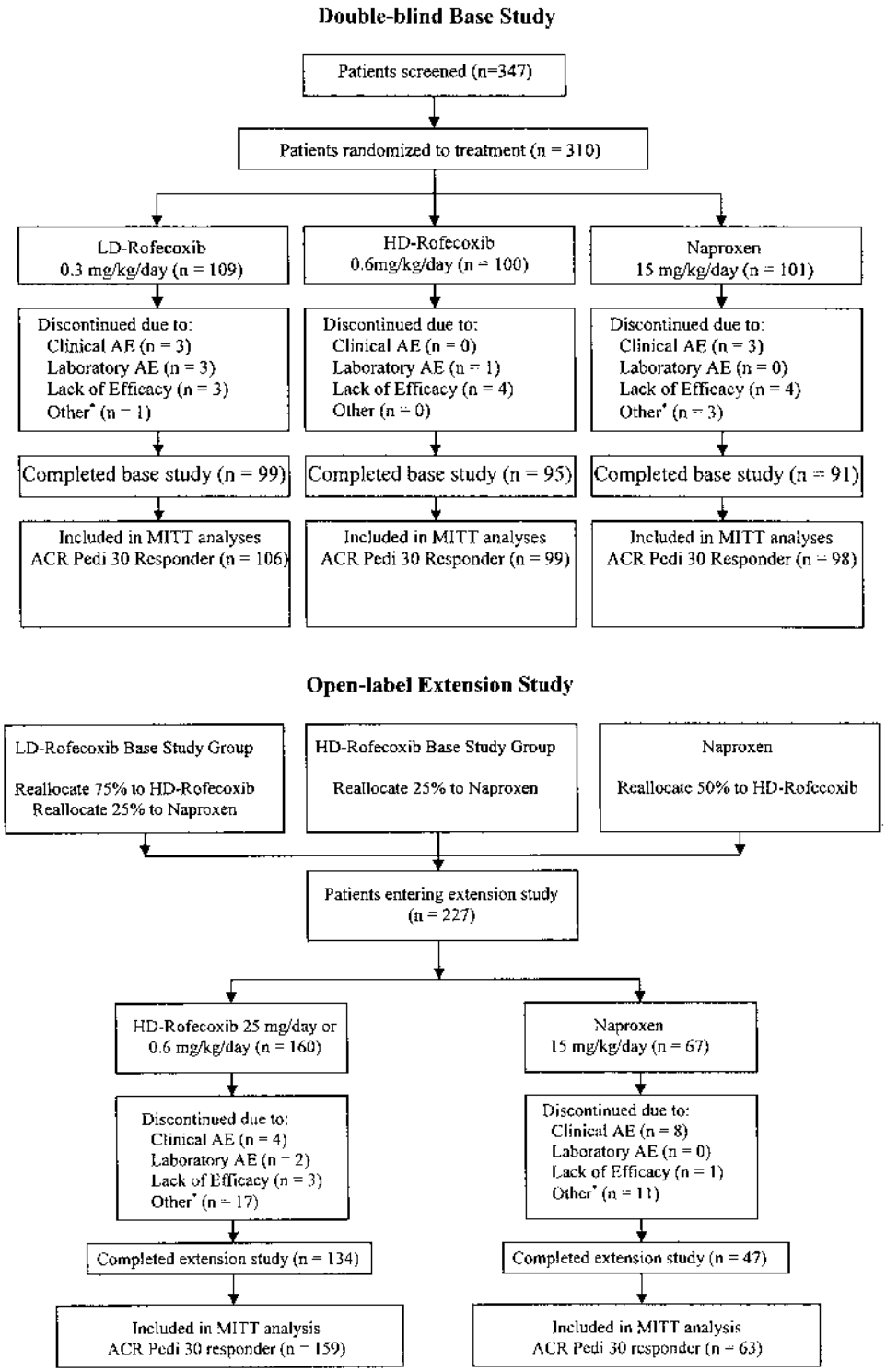

Figure 1. Patient disposition in the double-blind base and open-label extension studies. MITT: modified intent-to-treat; AE: adverse event. *Discontinued due to reasons other than those listed.

Efficacy assessments. The primary endpoint was the time-weighted average proportion of patients achieving an American College of Rheumatology Pediatric-30 (ACR Pedi 30) response[23,24]. The ACR Pedi 30 response is defined as at least a 30% improvement in any 3 of 6 variables in the core set of clinical measures, with no more than one of the remaining variables worsened by greater than 30%. Improvement in individual clinical measures was based on time-weighted average change from baseline across the treatment period. These 6 core components of the ACR Pedi 30 are: (1) Investigator's global assessment of disease activity (100 mm VAS); (2) Parent/Patient's Global Assessment of Overall Well-being (100 mm VAS); (3) a measure of physical functional ability, the Childhood Health Assessment Questionnaire (CHAQ; 0–3 point scale), was used; (4) number of joints with active arthri-

tis; (5) number of joints with limited range of motion; and (6) a laboratory measure of inflammation, the erythrocyte sedimentation rate (ESR) was used.

The key secondary endpoint was the proportion of patients that showed improvement from baseline in Parent/Patient's Assessment of Overall Well-being. The ACR Pedi 30 does not include a specific component for measurement of pain. For this reason, measurement of Parent/patient's global assessment of pain (100 mm VAS) was included as a secondary endpoint. Other secondary endpoints included the proportion of patients discontinuing due to lack of efficacy, and individual components of the ACR Pedi 30 definition of improvement.

Safety assessments. Clinical safety and tolerability were assessed based on physical examinations, Tanner stage, height and weight, clinical laboratory tests, and the collection of adverse experiences (AE) throughout the study. A serious AE was predefined as any AE that resulted in death, was deemed by the investigator to be life-threatening, or resulted in a persistent or significant disability or incapacity. Drug-related AE were those determined by the investigator to be possibly, probably, or definitely drug-related. Reported clinical AE in both the base and extension studies were screened for AE related to the known safety profile of traditional NSAID and COX-2 selective inhibitors. These included cardiorenal, hepatic, and skin and hypersensitivity AE. Blinded external adjudication committees were put in place prior to the initiation of the study to evaluate any potential thrombotic cardiovascular events or upper GI clinical events (i.e., upper GI perforation, ulcer, or bleeding) had they occurred during the trial.

Statistical analysis. The primary objective of the study was to compare the efficacy of rofecoxib to naproxen based on the comparison of ACR Pedi 30 response rates at the completion of the base and extension studies. The primary hypothesis was that the proportion of patients achieving an ACR Pedi 30 response would be similar between rofecoxib and naproxen treatment groups. The 95% confidence interval (95% CI) for the ratio of percentage of patients achieving an ACR Pedi 30 response (rofecoxib vs naproxen) was compared to 0.5, using a step-down procedure (HD-rofecoxib vs naproxen first, and if the lower 95% confidence bound was > 0.5, then the LD-rofecoxib response was analyzed). A lower 95% confidence bound > 0.5 indicated that the efficacy of rofecoxib was not inferior to that of naproxen.

Visual inspection of plots of the efficacy responses for continuous efficacy endpoints over the extension study, by base/extension treatment sequence, generally showed similar responses within each extension treatment group regardless of base study treatment assignment. Therefore, analyses for the extension were performed based on the treatment assigned for the extension study.

The sample size (N = 100 planned) per treatment group provided 99% probability that the observed lower 95% confidence bound for the ratio of the ACR Pedi 30 response rates would exceed 0.5, under the assumption that the true ACR Pedi 30 response rates for rofecoxib and naproxen were equal and exceeded 40% at Week 12.

The primary analysis was based on a modified intention-to-treat (MITT) analysis that included all patients with baseline observations and at least one on-treatment observation; a per-protocol analysis based on predefined exclusion rules was carried out for the primary endpoint to corroborate the primary analysis results (base study only). Dropouts were included in the primary analysis based on their responses obtained up to and including the time of discontinuation. Since most of the endpoints were analyzed based on the time-weighted averages over the treatment period, no missing values were imputed (i.e., data points were not carried forward) for the analysis of any endpoint.

Patients were excluded from the per-protocol analysis: if their Parent/Patient Assessment of Overall Well-being was < 10 mm or > 90 mm at the screening visit; if there were no active joints at allocation; or if a patient had an inflammatory joint disease, other than JRA, that confounded collection of efficacy data. Specific timepoints for a patient were excluded from the per-protocol analysis based on specific protocol violations between study visits: if the patient had taken < 70% of test medication since the previous visit; if the patient had not taken study medication on either of the 2 previous days prior to a study visit; or if the patient had undergone a change in analgesic, antiinflammatory, or other antirheumatic therapy that confounded subsequent efficacy measurements.

The proportion of patients achieving an ACR Pedi 30 response and the proportion of patients showing improvement from baseline in Parent/Patient's Assessment of Overall Well-being were assessed by the Mantel-Haenszel weighted estimate and resultant 95% CI for the ratio of rates with protocol, joint involvement (pauciarticular and polyarticular disease), and age group as stratification factors. No adjustments for multiplicity were made, as there was only one primary endpoint and the treatment comparisons were ordered. Since the ACR Pedi 30 is a composite measure, its individual components were examined singly to evaluate sources driving the composite results without multiplicity adjustments. Analysis of secondary endpoints was done in hierarchical order, starting with the key secondary endpoint, the proportion of patients demonstrating improvement from baseline in Parent/Patient's Assessment of Overall Well-being, thus obviating the need for multiplicity adjustment for those endpoints.

The proportion of patients discontinuing 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 treatment period, and analyzed using an analysis of covariance (ANCOVA) model including terms for treatment group, protocol stratum, joint involvement stratum (pauci, polyarticular course), and age group baseline values as covariates (i.e., as a linear regression parameter).

Consistency of treatment effects across subgroups for the primary endpoint was also explored. These subgroups included: joint involvement (i.e., pauci or polyarticular course); age group (≥ 2 years to ≤ 11 years of age; ≥ 12 years to ≤ 17 years of age); sex; Tanner stage; ethnicity; duration of JRA; baseline ESR; use of methotrexate (MTX) including MTX at baseline; low-dose corticosteroids; DMARD; or use of NSAID or naproxen prior to the study. Combined qualitative and quantitative interactions were assessed using the method of Gail and Simon[25] and the Mantel-Haenszel approach, respectively. Because of the large number of study sites, treatment-by-center interactions were not formally assessed since some study centers had only one patient. Therefore, study center effects for the ACR Pedi 30 and Parent/Patient's Assessment of Overall Well-being were examined visually using a listing of the sample sizes and raw mean treatment differences between groups across centers.

Safety and tolerability were assessed by comparing the percentages of patients in each treatment group who reported AE or exceeded predefined limits of change in laboratory measurements. Predefined limits of change from baseline were established for hemoglobin, hematocrit, serum alanine aminotransferase, serum aspartate aminotransferase, and serum creatinine; the proportion of patients outside the predefined limits was compared between active treatments. Prespecified safety analyses included the proportion of patients with: any AE, drug-related AE, serious AE, GI AE, laboratory AE, and the proportion of patients who discontinued due to an AE. For prespecified AE, the comparison among treatment groups was performed using Fisher's exact test, and a step-down procedure was used for comparisons of the 2 rofecoxib doses versus naproxen.

RESULTS

Patients. Of the 310 patients enrolled at the randomization visit, 285 (91.9%) completed the 12-week base study. Of these patients, 227 (73.2% of the initial study population) enrolled in the extension study. Overall, 10 (9.2%), 5 (5.0%), and 10 (9.9%) patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively, discontinued from the base study due to AE, lack of efficacy, or other reasons (Figure 1). A total of 160 patients received HD-rofecoxib and 67 patients received naproxen during the study extension. During the extension, 26 (16.3%) and 20 (29.8%) patients in the HD-rofecoxib and naproxen groups, respectively, discontinued due to AE, lack of efficacy, or other reasons (Figure 1). None of these differences was statistically significant.

Baseline patient demographic data are summarized in Table 1. No clinically meaningful differences were observed between treatment groups. The demographic characteristics of patients who entered the extension study were similar to those of patients who entered the base study (Table 1). Of the 310 patients enrolled in the base study, 227 (73.2%) were female and 225 patients (72.6%) were Caucasian. Patient ages ranged from 2 to 17 years (mean age 9.9 yrs). One hundred eighty-one (58.4%) patients were ≤ 11 years old and 46 (14.8%) were under age 5 years. The proportion of patients with pauci- and polyarticular involvement was similar between groups. Concomitant therapies were generally similar across the 3 treatment groups. The majority of patients had previously been treated with NSAID (88.7%), naproxen being the most widely used (56.1%). Sixty-four (20.6%) patients reported prior use of agents for acid-related disorders. Approximately half the patients were treated with DMARD; the most common DMARD was MTX (41.6%). Across treatment groups the rate of compliance for study medication was > 95% and > 98% in the base and extension studies, respectively.

Table 1. Baseline patient characteristics for the double-blind base and open-label extension studies.

	LD-Rofecoxib,	HD-Rofecoxib,	Naproxen,
Base Study	N = 109	N = 100	N = 101
Extension Study	NA*	N = 160	N = 67
Female, n (%)			
Base study	83 (76.1)	70 (70.0)	74 (73.3)
Extension study	NA	117 (73.1)	49 (73.1)
Age, mean (SD) yrs			
Base study	9.7 (4.3)	9.4 (4.3)	10.7 (4.0)
Extension study	NA	10.0 (4.1)	10.1 (4.4)
Age groups, n (%)			
2 to 11 yrs			
Base study	65 (59.6)	60 (60.0)	56 (55.4)
Extension study	NA	90 (56.2)	35 (52.2)
12 to 17 yrs			
Base study	44 (40.3)	40 (40.0)	45 (44.6)
Extension study	NA	70 (43.8)	32 (47.8)
Race, n (%)			
Caucasian			
Base study	85 (78.0)	69 (69.0)	71 (70.3)
Extension study	NA	116 (72.5)	46 (68.7)
Multiracial			
Base study	15 (13.8)	20 (20.0)	16 (15.8)
Extension study	NA	28 (17.5)	15 (22.4)
Other			
Base study	9 (8.2)	11 (11.0)	14 (13.9)
Extension study	NA	16 (10.0)	6 (9.0)
Joint involvement (%)			
Pauciarticular			
Base study	49 (45.0)	49 (49.0)	46 (45.5)
Extension study	NA	72 (45.0)	27 (40.3)
Mean duration of JRA, yrs (SD)			
Base study	4.0 (3.6)	3.4 (3.0)	3.7 (3.3)
Extension study	NA	3.7 (3.3)	2.9 (2.8)
History of medication, n (%)			
Corticosteroid			
Base study	21 (19.3)	22 (22.0)	15 (14.9)
Extension study	NA	30 (18.8)	13 (19.4)
DMARD user			
Base study	58 (53.2)	51 (51.0)	46 (45.5)
Extension study	NA	84 (52.5)	54 (80.6)
DMARD or corticosteroid user			
Base study	59 (54.1)	54 (54.0)	49 (48.5)
Extension study	NA	85 (53.1)	34 (50.7)
Methotrexate user			
Base study	49 (45.0)	40 (40.0)	40 (39.6)
Extension study	NA	71 (44.4)	29 (43.3)
Prior NSAID user			
Base study	95 (87.2)	90 (90.0)	90 (89.1)
Extension study	NA	144 (90.0)	58 (86.6)
Prior naproxen user			
Base study	61 (56.0)	56 (56.0)	57 (56.4)
Extension study	NA	92 (57.5)	36 (53.7)

NA: not applicable.

Efficacy

Base and extension studies. The percentages of patients 2–17 years old achieving an ACR Pedi 30 response during the base study were 46.2%, 54.5%, and 55.1% in the LD-rofecoxib, HD-rofecoxib, and naproxen treatment groups, respectively (Figure 2A). The ratio-of-response rates (RR) for rofecoxib compared to naproxen in the base study were 0.81 (95% CI 0.61, 1.07) and 0.98 (95% CI 0.76, 1.26) for LD- and HD-rofecoxib, meeting the prespecified criteria for non-inferiority to naproxen. Analysis of the per-protocol population corroborated these results with 53/97 (54.6%), 52/90 (57.8%), and 48/87 (55.2%) patients achieving an ACR Pedi 30 response in the LD-rofecoxib, HD-rofecoxib, and naproxen groups. Within the per-protocol population the RR for LD- and HD-rofecoxib compared to naproxen in the base study were 1.04 (95% CI 0.80, 1.35) and 0.96 (95% CI 0.73, 1.25), respectively. Examination of response rates within each age cohort revealed similar results, except in adolescents treated with LD-rofecoxib. In children (2–11 yrs), clinically comparable ACR Pedi 30 response rates of 50.8%, 55.9%, and 52.8% were observed in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. The RR for rofecoxib versus naproxen in children (2–11 yrs) were 0.96 (95% CI 0.67, 1.38) and 1.06 (95% CI 0.75, 1.49) in the LD and HD groups. In adolescents (12–17 yrs), the ACR Pedi 30 response rates were 39.5%, 52.5%, and 57.8% in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. The RR in adolescents for rofecoxib versus naproxen were 0.63 (95% CI 0.40, 0.99) and 0.88 (95% CI 0.60, 1.29) in the LD and HD groups. The RR for LD-rofecoxib in adolescents was close to the prespecified comparability bound. ACR Pedi 30 response rates were sustained and similar in the HD-rofecoxib (66.7%) and naproxen (60.3%) groups during the one-year extension [RR HD-rofecoxib vs naproxen 1.11 (95% CI 0.87, 1.41)], along with sustained improvement of each individual component of the ACR Pedi 30 criteria, as exemplified in a plot of cumulative ACR Pedi 30 response over time in patients receiving the same medication through 64 weeks (Figure 2B).

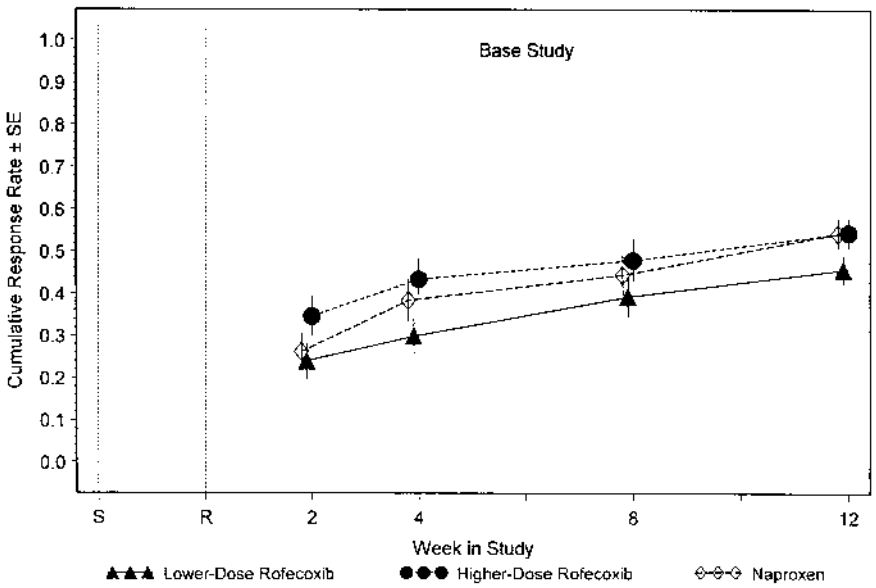

Figure 2A. Cumulative proportion of patients meeting ACR Pedi 30 criteria during the double-blind base study.

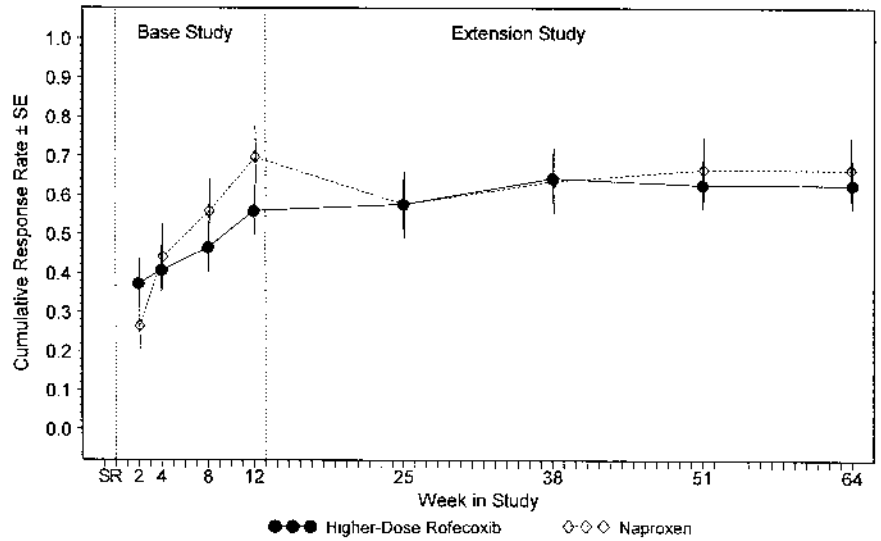

Figure 2B. Cumulative proportion of patients ages 2–17 years receiving the same therapy over 64 weeks meeting ACR Pedi 30 criteria in the double-blind base study and open-label extension study.

In the base study, the proportions of patients with improvement from baseline in Parent/Patient's Assessment of Overall Well-being were similar, with 74.3%, 76.0%, and 73.0% experiencing improvement in this endpoint in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. Patients (2–17 yrs) in the base study receiving LD- or HD-rofecoxib experienced numerically greater improvements in Parent/Patient Global Assessment of Pain (Table 2) compared to the naproxen group ($p = 0.065$). This difference between rofecoxib and naproxen reached statistical significance in children (2–11 yrs) receiving either dose of rofecoxib with least-square mean differences for change from baseline between LD-rofecoxib and naproxen of –8.51 mm (95% CI –14.81, –2.22; $p = 0.008$) and between HD-rofecoxib and naproxen of –8.12 mm (95% CI –14.52, –1.71; $p = 0.013$). In contrast, in adolescents the least-square mean differences for change from baseline for both rofecoxib doses compared to naproxen were not significant: 1.78 mm (95% CI –5.99, 9.55; $p = 0.652$) for LD-rofecoxib versus naproxen and –0.31 (95% CI –8.24, 7.61; $p = 0.938$) for HD-rofecoxib versus naproxen. The percentage of patients discontinuing due to lack of efficacy was similar in the LD-rofecoxib (2.8%), HD-rofecoxib (4.0%), and naproxen (4.0%) groups. Improvements in the ACR Pedi 30 core set of variables were generally similar to those observed for the

Table 2. Secondary efficacy endpoints and ACR Pedi 30 response component measures in the double-blind base study.

	LD-Rofecoxib, Baseline Mean[§]	LD-Rofecoxib, Mean Change from Baseline (95% CI)	HD-Rofecoxib, Baseline Mean	HD-Rofecoxib, Mean Change from Baseline (95% CI)	Naproxen, Baseline Mean	Naproxen, Mean Change from Baseline (95% CI)
Secondary endpoint						
Parent/patient global assessment of pain*	42.08	–12.50 (–15.98, –9.02)	41.85	–13.12 (–16.75, –9.48)	42.71	–8.43 (–11.98, –4.88)
ACR Pedi 30 component measures						
Parent/patient overall assessment of well-being*	39.50	–11.57 (–14.78, –8.36)	39.50	–12.08 (–15.44, –8.73)	43.83	–8.56 (–11.85, –5.27)
Investigator's global assessment of disease activity*	32.70	–12.45 (–14.95, –9.94)	35.77	–13.27 (–15.88, –10.65)	35.55	–12.05 (–14.60, –9.50)
CHAQ Index**	0.59	–0.11 (–0.18, –0.05)	0.56	–0.15 (–0.21, –0.08)	0.68	–0.12 (–0.18, –0.05)
No. of joints with active arthritis (total 68)	5.63	–2.36 (–2.96, –1.77)	6.52	–2.38 (–3.00, –1.75)	6.44	–2.74 (–3.35, –2.14)
No. of joints with limited range of motion (total = 70)	5.49	–0.54 (–1.15, 0.07)	5.86	–0.69 (–1.33, –0.06)	5.61	–1.71 (–2.33, –1.09)
ESR[†]	15.73	0.93[††] (0.82, 1.05)	17.57	0.85 (0.75, 0.96)	14.80	0.93 (0.82, 1.05)

* 0–100 mm visual analog scale. ** Child Health Assessment Questionnaire; 0–3 point scale. † Erythrocyte sedimentation rate; geometric mean mm/h. †† Least-squares mean ratio of on-treatment vs baseline. § Modified intent-to-treat population.

ACR Pedi 30 primary endpoint during the base study, except for the number of joints with limited range of motion, where a significantly better improvement was observed in the naproxen group compared to the LD-rofecoxib ($p < 0.05$) and HD-rofecoxib ($p < 0.01$) groups (Table 2). Additional exploratory analyses revealed that the treatment difference that was seen for this endpoint was likely caused by a few outliers. Overall, there appeared to be a numeric trend toward increased efficacy with HD-rofecoxib compared to LD-rofecoxib for all endpoints.

For the base study, analyses were also performed to assess the consistency of treatment effects for the primary endpoint among the patient subgroups displayed in Table 1. No significant qualitative interactions were observed among subgroups. A test for quantitative interactions revealed a statistically significant between-treatment interaction in the LD-rofecoxib group ($p = 0.035$) for history of prior NSAID use for the primary endpoint. In non-NSAID users at baseline, 3/14 (21.4%), 6/10 (60.0%), and 8/11 (72.7%) in the LD-rofecoxib, HD-rofecoxib, and naproxen groups achieved an ACR Pedi 30 response. Since only a small number (11.3%) of patients were not prior NSAID users at baseline, these results should be interpreted with caution and might be due to chance. There were also no apparent treatment-by-center interactions based on visual examination of tabulated data.

As with the primary endpoint, examination of secondary endpoints appeared to suggest that efficacy was maintained during the extension study in the HD-rofecoxib and naproxen groups, although no formal comparisons can be made due to the unblinded design of the extension period. Treatment responses for patients in the extension study who received the same treatment in the extension study as in the base study were evaluated. Among this group, 3 patients in the HD-rofecoxib group and one patient in the naproxen group discontinued due to lack of efficacy. A similar proportion of patients in the HD-rofecoxib (80.0%) and naproxen (75.4%) groups experienced an improvement from baseline in Parent/Patient's Assessment of Overall Well-being. Least-squares mean changes of the individual components of the ACR Pedi 30 endpoint from baseline for the 2 treatment groups were similar in this subset of patients, with sustained improvement through 64 weeks of therapy (Table 3).

Safety and tolerability

Both rofecoxib and naproxen were generally safe and well tolerated in the base and extension studies. Safety results for the base and extension studies are reported separately below.

Base study. Overall, there were no clinically significant differences in the percentages of patients across treatment groups experiencing any clinical AE or a drug related AE, or who discontinued due to an AE (Table 4). The 3 most commonly reported AE were abdominal pain, upper abdominal pain, and headache. GI AE occurred in 26.6%, 32.0%, and 39.6% of patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. The difference in incidence of GI AE in the LD-rofecoxib and naproxen groups did not reach statistical significance ($p = 0.056$). The numerically higher incidence of GI AE in the naproxen group was predominantly driven by a higher number of patients experiencing abdominal pain, 12.9%, compared to 6.4% and 6.0% in the LD-rofecoxib and HD-rofecoxib groups. When examined by age group, this trend was only observed in adolescents, as the rates of GI AE

Table 3. Secondary efficacy endpoint and ACR Pedi 30 response component measures over 64 weeks in patients receiving the same treatment in the double-blind base and open-label extension studies.

	HD-Rofecoxib, Mean Change from Baseline†, n = 60 (95% CI)	Naproxen, Mean Change from Baseline†, n = 35 (95% CI)
Secondary endpoint		
Parent/patient global assessment of pain*	–18.06 (–21.26, –14.87)	–16.55 (–21.84, –11.26)
ACR Pedi 30 component measures		
Parent/patient overall assessment of well-being*	–17.12 (–20.18, –14.06)	–15.80 (–20.90, –10.69)
Investigator's global assessment of disease activity*	–19.21 (–21.45, –16.98)	–16.80 (–20.47, –13.13)
CHAQ Index**	–0.26 (–0.32, –0.20)	–0.25 (–0.35, –0.15)
No. of joints with active arthritis (total 68)	–3.98 (–4.66, –3.30)	–3.61 (–4.72, –2.50)
No. of joints with limited range of motion (total = 70)	–1.84 (–2.51, –1.18)	–1.20 (–2.29, –0.11)
ESR***	0.78 (0.70, 0.86)	0.83 (0.70, 0.98)

* 0–100 mm visual analog scale. ** Child Health Assessment Questionnaire; 0–3 point scale. *** Erythrocyte sedimentation rate; least-squares mean ratio of on-treatment vs baseline; for ESR n = 59 for HD rofecoxib and n = 32 for naproxen. † Modified intent-to-treat population.

Table 4. Summary of safety data for the double-blind base study (12 weeks).

	LD-Rofecoxib, N = 109, n (%)	HD-Rofecoxib, N = 100, n (%)	Naproxen, N = 101 n (%)
No. of patients			
With any AE	72 (66.1)	61 (61.0)	63 (62.4)
With any drug-related* AE	21 (19.3)	22 (22.0)	28 (27.7)
With any serious AE	1 (0.9)	2 (2.0)	1 (1.0)
Discontinued due to an AE	3 (2.8)	0 (0.0)	3 (3.0)
Most common AE (> 5% in any group)			
Abdominal pain	7 (6.4)	6 (6.0)	13 (12.9)
Headache	6 (5.5)	5 (5.0)	13 (12.9)
Upper abdominal pain	7 (6.4)	12 (12.0)	7 (6.9)
Nasopharyngitis	11 (10.1)	10 (10.0)	1 (1.0)
Pyrexia	5 (4.6)	4 (4.0)	9 (8.9)
Diarrhea	5 (4.6)	7 (7.0)	4 (4.0)
Pharyngitis	7 (6.4)	3 (3.0)	3 (3.0)
Vomiting	7 (6.4)	3 (3.0)	3 (3.0)
Upper respiratory tract infection	6 (5.5)	6 (6.0)	7 (6.9)
Nausea	3 (2.8)	4 (4.0)	6 (5.9)

* Determined by investigator to be possibly, probably, or definitely drug-related. AE: adverse event.

were similar across groups in the children 2–11 years old. Drug related AE occurred most frequently in the GI system and were similar among the 3 treatment groups. Two patients in the LD-rofecoxib and one patient in the naproxen group discontinued due to GI AE. The incidences of serious clinical AE, none of which was drug related, were one (0.9%), 2 (2.0%), and one (1.0%) in the LD-rofecoxib, HD-rofecoxib, and naproxen treatment groups. The serious clinical AE reported in the rofecoxib groups all involved a worsening of JRA symptoms. One of these patients, in the LD-rofecoxib group, discontinued as a result of this AE. The one serious AE in the naproxen group was due to gastroenteritis resulting in hospitalization. This patient also experienced generalized lymphadenopathy, fever, and anemia secondary to her underlying JRA.

No clinical AE of hypertension, congestive heart failure, renal insufficiency, or related terms were identified in the base study. However, there were 2 AE consistent with edema. One case of edema in the HD-rofecoxib group was determined by the investigator to be drug related. The case of edema in the naproxen group was determined not to be drug related by the investigator. Both patients completed the base study. There were no reported cases of serious upper GI events (i.e., perforations, ulcers, bleeds) or thrombotic cardiovascular events in either the base or extension studies.

Mild to moderate allergic-type skin and hypersensitivity reactions occurred in 5 (4.6%), 5 (5.0%), and 4 (4.0%) patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. Two of these events, one each in the HD-rofecoxib and naproxen groups, were considered drug related by the investigator. One patient in the HD-rofecoxib group had 3 mild cases of exanthem, lasting 8 hours. One patient in the naproxen group had a mild rash that lasted 12 hours.

In the base study, laboratory AE involving the liver occurred in 8 patients — 4 (3.5%), 2 (2.0%), and 2 (1.9%) patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. All 8 patients had laboratory AE of increased ALT and/or AST. Three of these 8 patients, 2 (1.7%) in the LD-rofecoxib and one (1.0%) in the HD-rofecoxib group, exceeded the predefined limits of change for ALT and AST. In general, the increases in ALT and AST in these 8 patients resolved either upon discontinuation of study medication or with continued therapy. In one of these 8 patients, who was in the naproxen group, ALT values declined but did not normalize with continued treatment, with the highest value recorded following completion of the base study. This patient did not enroll in the extension study. It is of interest that of these 8 patients, 3 (2.6%) in the LD-rofecoxib and 2 (2.0%) in the HD-rofecoxib group were taking concomitant MTX. No patient in the base study had evidence of hepatic dysfunction or associated clinical AE. Only one patient, in the naproxen group, experienced an elevation of serum creatinine above the predefined limits of change.

Extension study. In the open-label extension, there was a similar incidence of clinical AE in the HD-rofecoxib and naproxen groups. The incidence of drug related AE and serious AE was numerically higher in the naproxen group compared to the HD-rofecoxib group (Table 5). There was one drug related case of pseudoporphyria in the HD-rofecoxib group. A significantly larger percentage of patients discontinued due to AE in the naproxen group compared to HD-rofecoxib (11.9% vs 2.5%; p = 0.007). Similar to the base study, a numerically higher percentage of patients in the naproxen group experienced a GI related AE. Among those patients, a significantly higher percentage in the naproxen group discontinued due to a GI AE (7.5% vs 1.3%; p = 0.025).

As with the base study, no clinical AE of hypertension, congestive heart failure, renal insufficiency, or related terms were observed. In addition, no elevations of serum creatinine were observed. However, one patient in the HD-rofecoxib group developed poststreptococcal glomerulonephritis. Three cases of edema were reported, all in the HD-rofecoxib group. One case was determined to be possibly drug related and one case probably drug related by the investigator.

Mild to moderate allergic-type skin and hypersensitivity reactions occurred in 4 (2.5%) patients in the HD-rofecoxib and 4 (6.0%) in the naproxen group. None of these AE was considered drug related or resulted in discontinuation of study drug. They consisted of a reactogenicity response at the site of immunization injection, allergy to penicillin, trauma, rheumatoid rash, and a rash of unknown origin.

Table 5. Summary of safety data for the open-label extension study (52 weeks).

	HD-Rofecoxib, N = 160, n (%)	Naproxen, N = 67 n (%)
No. of patients		
With any AE	119 (74.4)	52 (77.6)
With any drug-related* AE	19 (11.9)	13 (19.4)
With any serious AE	10 (6.3)	7 (10.4)
Discontinued due to an AE	4 (2.5)	8 (11.9)
Discontinued due to a drug-related AE	2 (1.3)	5 (7.5)
Most common AE (> 5% in any group)		
Abdominal pain	10 (6.2)	4 (6.0)
Headache	24 (15.0)	8 (11.9)
Upper abdominal pain	11 (6.9)	8 (11.9)
Nasopharyngitis	11 (6.9)	9 (13.4)
Pyrexia	10 (6.2)	7 (10.4)
Diarrhea	3 (1.9)	6 (9.0)
Pharyngitis	11 (6.9)	9 (13.4)
Gastroenteritis	9 (5.6)	2 (3.0)
Upper respiratory tract infection	20 (12.5)	4 (6.0)
Acute bronchitis	3 (1.9)	6 (9.0)
Cough	3 (1.9)	7 (10.4)
Anemia	11 (6.9)	7 (10.4)

* Determined by investigator to be possibly, probably, or definitely drug-related. AE: adverse event.

There were no clinically important differences in laboratory AE between treatment groups. Eleven patients had laboratory AE of increased AST or ALT or exceeded the predefined limits of change for ALT and/or AST — 9 (5.6%) patients in the HD-rofecoxib and 2 (9.0%) in the naproxen group. These patients fell into 2 distinct categories of hepatocellular abnormalities. In the first category, patients had biochemical abnormalities, including increased ALT and AST as well as increases in bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase. There were 5 patients in this category — 3 (1.9%) taking HD-rofecoxib and 2 (3.0%) naproxen. All 5 of these patients had associated clinical AE. Two patients, both in the naproxen group, had clinical AE of hepatitis A. Both these patients exceeded the predefined limits of change of ALT and AST. One patient in the HD-rofecoxib group developed hepatomegaly, another developed hepatitis A, and one patient had a clinical course consistent with acute Epstein-Barr virus infection. The second category included those patients, all in the HD-rofecoxib group, whose abnormalities were similar to those found in the base study, namely, isolated increases in ALT and/or AST without associated evidence for hepatic dysfunction. Three of these patients resolved while on continued therapy, 2 resolved by the poststudy visit, and one did not resolve by the poststudy visit. Due to the unbalanced treatment allocation in the extension study, it is most likely that the incidence of these abnormalities is underrepresented in the naproxen group.

DISCUSSION

Treatment with rofecoxib (low-dose and high-dose) or naproxen resulted in comparable percentages of ACR Pedi 30 treatment responses in patients 2 to 17 years old with pauci- or polyarticular course JRA. There was a numerically greater ACR Pedi 30 response rate with HD-rofecoxib compared to LD-rofecoxib in adolescents following 12 weeks of therapy suggestive of a dose response. In adolescents the ACR Pedi 30 treatment response to LD-rofecoxib was inferior to that in the naproxen group. However, the Parent/Patient's Global Assessment of Pain in both rofecoxib groups showed a numeric trend toward better pain relief compared to naproxen. In contrast, within the ACR Pedi 30 core set of variables, a significant improvement in the number of joints with limited range of motion was observed in the naproxen group compared to both rofecoxib groups. The results from the extension study indicate that the efficacy of both rofecoxib and naproxen is maintained through 64 weeks of therapy. However, the interpretation of the results from the extension study has several important limitations that should be kept in mind. The extension was an open-label study, the numbers of patients in each treatment group were not balanced, and it included a preselected study population.

Successful management of JRA remains a significant clinical challenge despite the availability of a number of antirheumatic therapies. Current treatment paradigms often

involve multimodal therapy with agents acting by different mechanisms of action[4,5]. Unfortunately, some agents exhibit overlapping toxicity, such as the increased risk of GI AE associated with traditional NSAID, corticosteroids, leflunomide, and MTX. The frequent utilization of multimodal therapy is evident in the substantially high number of patients in our study receiving multiple concomitant antirheumatic medications. Traditional NSAID have been shown to be valuable components of multimodal regimens for the treatment of JRA[4]. COX-2 selective inhibitors such as rofecoxib, which demonstrate a reduced relative risk of upper and lower GI AE, may therefore offer an advantage over traditional NSAID when used in multimodal regimens with other antirheumatic therapies. Appropriately designed clinical studies will be required to conclusively demonstrate significant reductions in the relative risk of adverse GI events in multimodal regimens containing COX-2 selective inhibitors in pediatric populations.

Overall, both rofecoxib and naproxen appeared to be generally safe and well tolerated in this pediatric population. The incidence of AE involving the liver was low and similar to that described in adult patients with RA treated with rofecoxib or naproxen. Not unexpectedly, the majority of patients with hepatocellular abnormalities were also being treated with MTX. With regard to renovascular safety, 3 drug related cases of edema were observed, all in the HD-rofecoxib group. No clinical AE of hypertension, congestive heart failure, or renal insufficiency were identified in the base study and open-label extension study. Additionally, there were no reported serious thrombotic cardiovascular AE or serious upper GI events in this study. However, in light of recent longterm placebo-controlled chemoprevention studies in adults, showing an elevated relative risk of thrombotic cardiovascular events compared to placebo following longterm use of rofecoxib and celecoxib[26,27], the longterm cardiovascular safety of COX-2 selective inhibitors and traditional NSAID in pediatric patients will need to be assessed further.

The ACR Pedi 30 definition of response[23,24] is similar in concept to the ACR20 response criteria, which were designed to provide standardization for comparing efficacy responses between adult RA treatments, although power to discriminate therapies may be reduced in studies using dichotomous endpoints compared to the use of continuous measurements[28]. The rates of ACR Pedi 30 responses observed in all treatment groups in our study are well above the pooled composite placebo response rate of 28.9% across 6 placebo-controlled trials previously reported by others[29]. This and several recent studies provide additional insight regarding the performance of the ACR Pedi 30 definition of improvement in the assessment of NSAID. The ACR Pedi 30 definition of improvement was originally developed to assess polyarticular disease. Although 2 of the 6 components of the ACR Pedi 30 involve joint counts, possibly creating a slight bias when used for pauciarticular disease, our data show that the endpoint appears to provide discriminant value for patient treatment with COX-2 selective inhibitors or traditional NSAID. Specifically, its use allowed us to detect a numeric trend for an increased response rate with an increasing dose of rofecoxib and non-inferiority to the median dose of naproxen used to treat JRA in the United States. Our results lend further support for the use of the ACR Pedi 30 as a primary endpoint in clinical studies designed to compare therapies directly.

Only one other study has used the ACR Pedi 30 endpoint to examine the efficacy of a NSAID for treatment of JRA. A recently published study directly compared the ACR Pedi 30 response of the partially selective COX-2 inhibitor meloxicam to naproxen 10 mg/kg/day in patients with JRA 2–16 years of age with pauci- or polyarticular disease[30]. In that study, the dose of naproxen was two-thirds the dose used in our study. The study was also specifically designed as a superiority study, unlike our non-inferiority study design. In that study, using the ACR Pedi 30 response endpoint, meloxicam 0.125 and 0.25 mg/kg/day both failed to show superiority to naproxen 10 mg/kg/day.

We have demonstrated that daily treatment for 12 weeks with rofecoxib up to 12.5 or 25 mg, or naproxen 15 mg/kg/day up to 1000 mg per day, provides comparable clinically significant efficacy for the treatment of pauci- and polyarticular course JRA in patients as young as 2 years of age. Continued treatment with HD-rofecoxib or naproxen 15 mg/kg/day in an open-label extension over an additional 52 weeks provided comparable sustained efficacy. Both rofecoxib and naproxen were generally well tolerated in children as young as 2 years of age throughout the study. For patients with JRA, effective analgesics formulated as oral suspensions with once-daily dosing schedules can no doubt help simplify the multimodal treatment regimens that they often require. Although rofecoxib was voluntarily withdrawn from the worldwide market in September 2004, the results from this trial provide valuable information regarding the design and performance of randomized clinical trials in JRA, and the therapeutic potential of COX-2 selective inhibitors for the treatment of pediatric patients with juvenile rheumatoid arthritis.

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