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	(b) (4)
Submission Type	SE5 (Different/New Population) Labeling Changes with New Indications in Pediatric Populations Pediatric Exclusivity Determination Requested

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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. (b) (4) here 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 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 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).

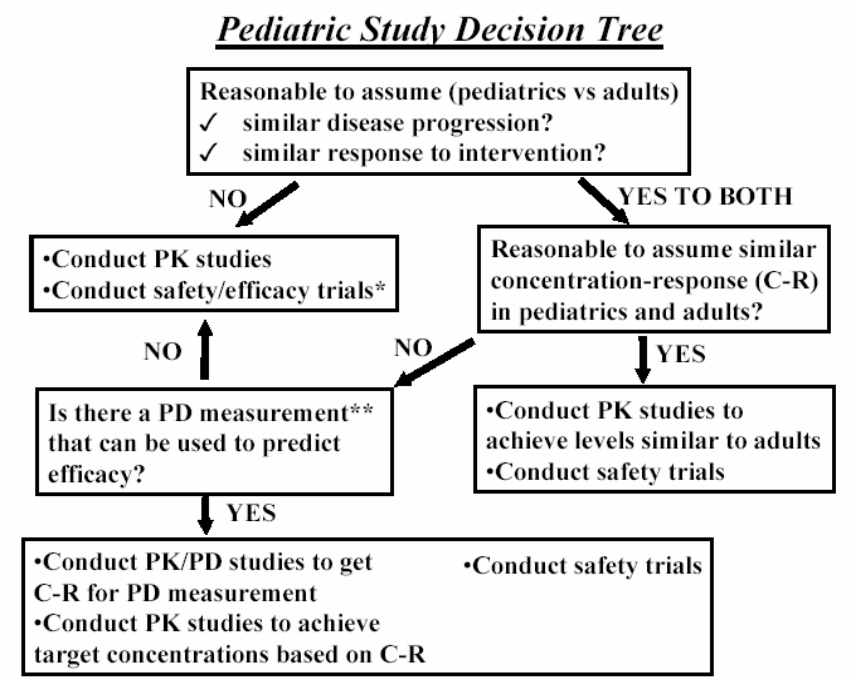
Table 1.3.2. Comparison of Dose-adjusted AUC(0-24hr) † (ng·hr/mL) for Pediatric Patients to Adults.

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



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. Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- No. There are 3 types of JRA: pauciarticular, polyarticular, and systemic. Only RF+ polyaritcular JRA is similar to RA in adults. Also one has to consider the effect of 10-20 years of continuous use of NSAIDs on renal function in the adult population, an experience that the newly diagnosed pediatric JRA patients would not have.

2. Is it reasonable to assume that pediatric patients are similar to adults with regard to response to intervention?

- Yes.

Because only one "Yes" to two questions in Box 1, the Pediatric Study Decision Tree suggests:
- Conducting PK studies
- Conducting safety and efficacy trials

These studies were performed by the Sponsor.

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.

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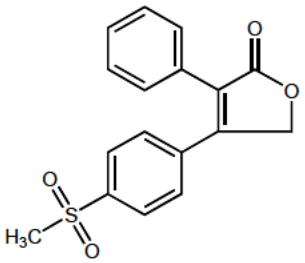
OCPB briefing (Required Office-Level) was held on May 24, 2004.

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 12.5 mg/5 mL oral suspension (2.5 mg/mL) is recommended.

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	2263.8	13377	1.07	(0.91, 1.26)
6- to 11-year old	13	5700.1	5656.7	3753.0	9142.2	1.25	(1.04, 1.52)
12- to 17-year old	11	4928.4	5164.0	3300.0	7308.0	1.08	(0.89, 1.32)
Pediatric Patients	45	5102.2	5047.7	2263.8	13377	1.12	(0.98, 1.29)
Healthy Adults	26	4543.4	4712.2	2324.1	8439.0		

† 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	2263.8	13377	0.73	(0.59, 0.90)
6- to 11-year old	13	5700.1	5656.7	3753.0	9142.2	0.86	(0.68, 1.08)
12- to 17-year old	11	4928.4	5164.0	3300.0	7308.0	0.74	(0.58, 0.94)
Pediatric Patients	45	5102.2	5047.7	2263.8	13377	0.77	(0.64, 0.93)
RA Adults	12	6642.4	6584.3	3689.0	11934		

† 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.

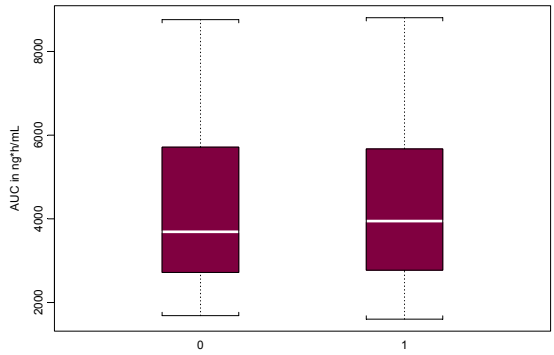
Dose	Response Rate	Rofecoxib/Naproxen (95% CI)
Lower-Dose Rofecoxib[a]	(b) (4)	
Higher-Dose Rofecoxib[b]	54.5%	0.99 (0.76, 1.28)
Naproxen (15 mg/kg/day)	55.1%	

[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. (b) (4)

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.

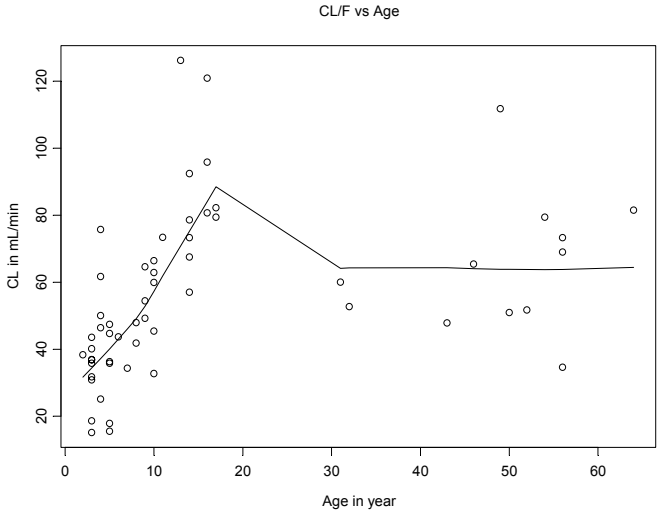
2.3 Intrinsic Factors

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).

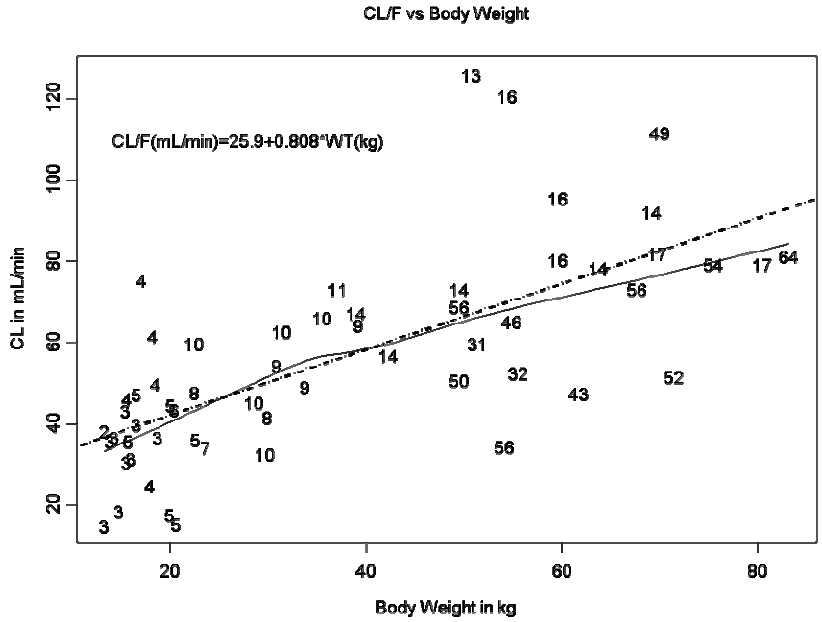


Dots represent the individual CL/F and line represents the lowess regression line

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 individual'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 = $0.007184 \bullet (\text{height}^{0.725}) \bullet (\text{weight}^{0.425})$, where height is in cm, weight is in kg and BSA is given in m^2.

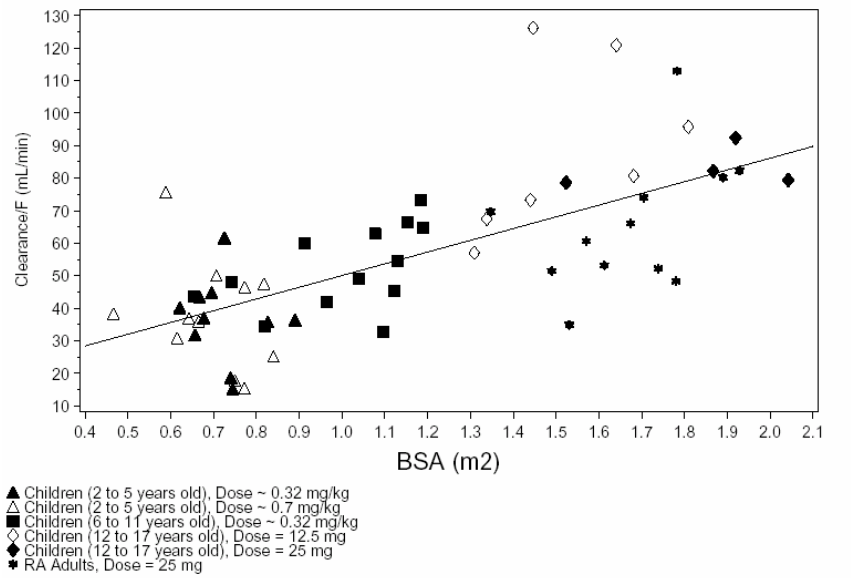


Figure 2.3.1.3. Relationship Between CL/F and Body Surface Area (m^2) in JRA Patients Aged 2 to 12 years, JRA patients Over 12, Healthy Adults Subjects and Adult RA Patients.

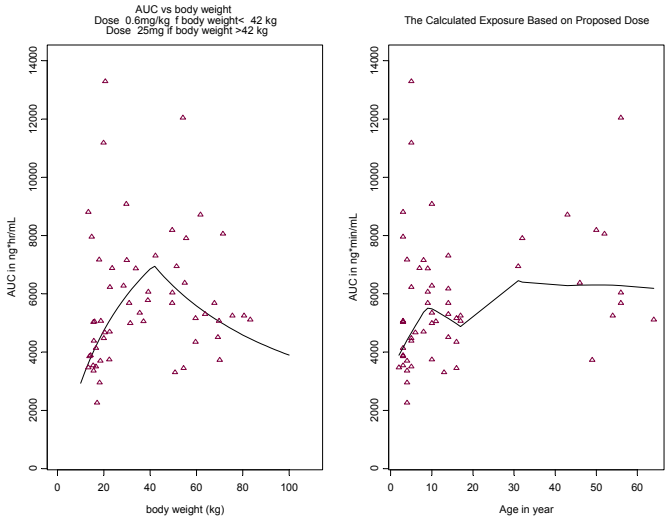
Gender:
Examination of oral clearance by sex revealed no difference between genders, consistent with what have been found in adults.

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 of 0.6 mg/kg for patients 2 to 11 years old (up to 25 mg) and 25-mg doses for all others (adolescents and adults). 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 P105, P109c and P109c2 were analyzed in accordance with protocol DM-406 B. Plasma samples for P228 were analyzed in accordance with protocol DM-406 B 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	Drug Metabolism Department, Merck & Co., Inc., West Point, PA 19486
Compound	Rofecoxib
Internal Standard	L-755100
Matrix	Plasma
Accuracy	93.6 % - 105.8 %
Precision (CV%) *Interday*	0.7%-7.5%
Standard curve range	0.5-80 ng/mL ($R^2 > 0.999$)
Sensitivity (LOQ)	0.50 ng/mL
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)

3 DETAILED LABELING RECOMMENDATIONS

(Underlines represent added text and strikethroughs represent deleted text.) Please refer to Dr. Yancey's review for recommended changes to the "Clinical Studies" and "Adverse Reactions" sections of the labeling and Patient Package Insert (PPI). At the time of this review, labeling negotiation is on-going. Please refer to the final approval letter for final version of the Package Insert (PI) and PPI.

CLINICAL PHARMACOLOGY

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 based on geometric means was 1.67. The $AUC_{0\text{-}24hr}$ 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).

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.

(b) (4)

Pediatric

The steady state pharmacokinetics of rofecoxib was evaluated in patients (b) (4) 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 (b) (4) years of age was similar to that of healthy adults and higher than that of adult RA patients (Table 1). The apparent clearance after oral administration of rofecoxib in patients (b) (4) 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). (b) (4)

(b) (4)

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

	JRA patients	Adults
(b) (4)		

*Pauciarticular and polyarticular course JRA

(b) (4)

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 (oligoarticular) or polyarticular course juvenile rheumatoid arthritis in patients (b) (4)

For the management of acute pain in adults.

For the treatment of primary dysmenorrhea.

PRECAUTIONS

Pediatric Use

The use of VIOXX in patients with pauciarticular (oligoarticular) or polyarticular course JRA ≥ 2 years to ≤ 17 years of age (b) (4) was studied in (b) (4) pharmacokinetic studies and (b) (4) a 12-week, double-blind active- (b) (4) controlled study with a (b) (4) 52-week open-label extension. (See CLINICAL PHARMACOLOGY, *Pediatric;* CLINICAL STUDIES, *Pediatric Patients, Pauciarticular and Polyarticualr CourseJuvenile Rheumatoid Arthritis (JRA);* ADVERSE REACTIONS, (b) (4) *Pauciarticular and Polyarticualr Course JRA.*)

Rofecoxib has not been studied in patients under the age of 2 years or with body weigh less than 10 kg.

DOSAGE AND ADMINISTRATION

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

(b) (4)

* Oral suspension dosage form is recommended. To improve dosing accuracy, (b) (4)

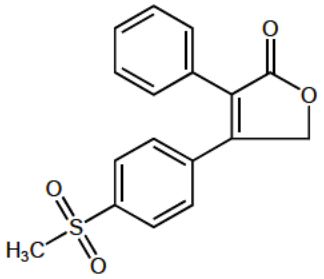
4 APPENDICES

4.1 Proposed Package Inserts from the Sponsor

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

* Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

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

4.2 Individual Study Review

4.2.1 Adult RA Patients (Protocol 228)

A Single-Period Multiple-Dose Study in Rheumatoid Arthritis Patients to Investigate the Steady-State Plasma Concentration Profile of Rofecoxib (Protocol 228)

Study Period (Clinical Portion): May 1, 2003 to June 29, 2003

Principle Investigators: Thomas C. Marbury MD
4401 S. Orange Ave., Suite 108
Orlando, FL 32806

Randall R. Stoltz MD
800 St. Mary's Drive,
Evansville, IN 47714

Study Centers: Two study sites in the U.S (Orlando Clinical Research Center and GFI Research Center)

Analytical Sites: Drug Metabolism Department, Merck & Co., Inc., West Point, PA 19486

Rationale for Present Study: In the Written Request, it is FDA's opinion that the proper comparison to children with juvenile rheumatoid arthritis (JRA) would be adults with RA. Therefore PK data from a prespecified RA database is needed for comparison to PK data from the JRA group. This study provided information on the steady-state pharmacokinetics of rofecoxib in RA patients. Pharmacokinetic data from this protocol will be used to compare with the pharmacokinetic data in children with JRA. Data from this study could also be used to compare with the historical PK data from healthy adults.

Objectives: To assess the pharmacokinetics of rofecoxib 25 mg once daily at steady state after 10 days treatment in rheumatoid arthritis (RA) patients.

Study Design: This was an open-label, single-period, multiple-dose study in which RA patients received rofecoxib 25 mg once daily in the morning (between 0700 and 1030) for 10 days. The 10-day treatment period in this study was sufficient to attain the steady-state plasma concentrations of rofecoxib. Previously, in tablet formulation studies, subjects, on average, reached steady state by Day 4; all subjects were expected to reach steady state prior to Day 10. This is consistent with a mean accumulation half-life of 16.7 hours.

Men and non-pregnant women, 21 to 65 years of age, who satisfied at least 4 of 7 American Rheumatism Association revised criteria (1987) for the diagnosis of rheumatoid arthritis, within 40% of ideal body weight, who agreed to follow the study procedures were enrolled in the study.

Patients fasted from all food and drink except water for at least 10 hours and 4 hours prior to dosing on Day 1 and Days 5 through 9, respectively. Patients fasted from all food and drink except water for at least 10 hours prior to dosing on Day 10. Rofecoxib 25-mg final market image tablets were given with 8 ounces of water. Subjects were instructed by the investigator not to eat nor drink anything, including water, for 2 hours following the rofecoxib dose.

Patients had predose blood samples taken on Day 1 and Days 5 through 10. On Day 10, blood samples for plasma rofecoxib concentrations were obtained over 24 hours postdose.

Subjects: Fourteen RA patient subjects (2 males, 12 females) were enrolled into this study (Table 1). All subjects were Caucasians. 12 subjects completed the study. For these 12 subjects, the mean age was 49.1 years with a range of 31 to 64 yrs old. The mean weight was 62 kg with a range of 49.5 to 83.2 kg, and the mean height was 163.8 cm with a range of 160 to 173 cm. Subjects 0014 and 0015 discontinued due to clinical adverse experience and other reasons.

Table 1. Baseline Patient Characteristics.

Allocation Number	Gender	Age (Years)	Height (cm)	Weight (kg)	Race
0101	M	54	172.7	75.5	white
0102	F	46	173	54.9	white
0103	F	43	168.9	61.7	white
0013	F	56	163.8	67.7	white
0014	F	40	157.5	56.4	white
0015	F	39	162.6	51.8	white
0016	F	31	160	51.4	white
0017	F	50	161.3	49.5	white
0018	F	32	162.6	55.5	white
0019	F	49	160	70	white
0114	F	56	165.1	49.55	white
0115	M	64	167.6	83.2	white
0020	F	56	163.8	54.1	white
0021	F	52	163.8	71.4	white
Total:					
Mean	M	59	170.2	79.4	N/A
	F	46	163.5	57.8	N/A
	M and F	48	164.5	60.9	N/A
Range	M	54-64	167.6-172.7	75.5-83.2	N/A
	F	31-56	157.5-173	49.5-71.4	N/A

Test Product Information: Rofecoxib 25 mg tablets; formulation number E10102; clinical batch number 013485V. The tablet formulation number E-10102 had the same composition as the marketed product; however, the tablets were in the clinical plain image not the debossed market image.

Sample Collection for PK Measurement:
Days 1, 5 through 10: Predose
Day 10: Predose, 0.5, 1, 2, 3, 4, 5, 6, 7.5, 9, 10, 12, 14, 18, and 24 hours postdose.

Sample Analysis: Plasma samples were assayed for rofecoxib concentrations by the Merck & Co., Inc., Drug Metabolism Department. Plasma samples were analyzed in accordance with protocol DM-406 B with minor modifications: (1) injection volume was decreased from 135 µL

to 50 µL; (2) samples were eluted into a 96-well collection plate; (3) samples were mixed with an 8-channel pipet and (4) samples were transferred to the autosampler in a 96-well collection plate. The analytical method utilized solid-phase extraction in a 96-well format and reversed-phase HPLC with post-column photochemical derivatization. The photolysis products of the drug and internal standard (L-000755100) were detected using a fluorescence detector. The lower limit of quantification (LLOQ) for MK-0966 in plasma was 0.5 ng/mL. The detailed bioanalytical report is included in Reference P228, Appendix 2.1.

Pharmacokinetic and Statistical Analysis: Plasma rofecoxib concentrations were used to estimate the PK parameters (trough concentrations, AUC_{0-24}, C_{max}, T_{max}) for each patient. These parameters were assessed to evaluate the plasma concentration profiles (trough concentrations, AUC_{0-24} and C_{max}) and time-to-peak plasma concentrations (T_{max}) at steady state following multiple doses of rofecoxib 25-mg tablet in adult RA patients.

Summary statistics for the trough concentrations, AUC_{0-24} , C_{max}, CL/F, and T_{max} were provided with a 90% confidence interval (CI), based on the t-distribution. The AUC_{0-24} , C_{max}, and CL/F were log transformed.

Pharmacokinetic Results of Adult RA Patients:

Steady State Assessment

C_{trough} values of rofecoxib did not change from Days 5 to Day 10 suggesting that steady-state was reached by Day 5 (Table 2).

Table 2. Summary Statistics for Trough Concentrations (ng/mL) Following Multiple Oral Dose Administration of Rofecoxib in Adult RA Patients.

Days on Study Medication	N	Mean	Median	Min Max	Between-Subject SD	90% CI
4	12	184.5	171.1	65.13, 301.46	76.9	(144.61, 224.34)
5	12	179.1	181.2	76.03, 295.78	67.2	(144.25, 213.88)
6	12	180.4	163.5	67.89, 317.7	76.2	(140.93, 219.91)
7	12	191.5	184.6	68.32, 368.53	84.3	(147.76, 235.20)
8	12	197.4	211.3	71.51, 364.46	83.5	(154.15, 240.69)
9	12	191.0	182.1	68.00, 356.67	87.4	(145.64, 236.29)

SD= Standard Deviation.
CI=Confidence Interval.

Pharmacokinetics of Rofecoxib in Adult RA Patients

Table 3. Individual Pharmacokinetic Parameters Observed at Steady State in Adult RA Patients Administered Rofecoxib 25 mg q.d. for 10 Days.

AN	$AUC_{24\ hr}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	Cl/F (mL/min)
101	5196	396.9	3	79.4
102	6305	582.4	3	65.4
103	8625	564.0	3	47.8
13	5626	565.2	3	73.3
114	5980	446.3	3	69.0
115	5062	306.2	1	81.5
16	6876	496.7	4	60.0
17	8108	536.0	4	50.9
18	7832	452.9	5	52.7
19	3689	307.3	1	111.8
20	11934	902.1	4	34.6
21	7976	668.7	4	51.7

The $AUC_{0\text{-}24\ hr}$ geometric mean with corresponding 90% CI was 6642.4 ng·hr/mL (3382.21, 13045.4). The C_{max} geometric mean with corresponding 90% CI was 496.6 ng/mL (252.1, 978.2). The CL/F geometric mean with corresponding 90% CI was 62.1 mL/min (52.98, 72.80). Summary statistics for $AUC_{0\text{-}24\ hr}$, C_{max} and CL/F are listed in Table 4.

Table 4. Summary Statistics for $AUC_{0\text{-}24\ hr}$ (ng·hr/mL), C_{max} (ng/mL), and CL/F (mL/min) Following Multiple Oral Dose Administration for 10 Days of Rofecoxib Therapy to Adult RA Patients (N=12).

Parameter	Geometric Mean†	Median†	Min and Max†	Between-Subject SD†	90% CI†
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	6642.4	6584.3	3689.0, 11934.0	4426.1	(3382.2,13045.4)
C_{max} (ng/mL)	496.6	516.0	306.2, 902.1	331.1	(252.1, 978.2)
CL/F (mL/min)	62.1	62.6	34.6, 111.8	41.4	(52.98, 72.80)

† Back-transformed from the log scale.
SD= Standard Deviation.
CI=Confidence Interval.

Comparison of PK Parameters for Adult RA Patients and Healthy Adults:
Compared to historical PK data from healthy adults (P042 and P043), rofecoxib showed lower clearance in RA patients with mean $AUC_{0\text{-}24}$ increased 46% and C_{max} increased 38%, respectively (Table 5). RA patients in this study weighed less than healthy adults in previous PK studies (mean weight 62 kg vs. 77.7 kg). Because CL/F of rofecoxib increases with body weight, weight difference may contribute to lower apparent oral clearance of rofecoxib in RA patients

from this study than clearance in historical healthy adults in addition to disease and medical history factors. This difference in body weight may also be due to the preponderance of females present in this study vs. the other studies with healthy adults using a more balanced population.

Table 5. Comparison of PK Parameters for Adult RA Patients and Healthy Adults.

	Mean Weight (kg) (range)	N	Mean AUC_{0-24} (ng·hr/mL)	Mean C_{max} (ng/mL)	Mean CL/F (mL/min)	T_{max} (hr)
RA Pateints (P228)	62.0 (49.5, 83.2)	12	6642	497	62.1	3
Healthy Adults (P042, P043)	77.7 (52.3, 104.5)	26	4543	361	92.4	3.2

PK dataset for adult RA patients for this study 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) (Mean age and gender were similar between PK and clinical trials, 49 years vs. 55 years and 86% women vs. 79% women, respectively). Because CL/F of rofecoxib increases with body weight, the oral clearance for these 12 PK patients may be lower than that in the RA population in the clinical trial and thus 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. Based on relationship between CL/F and body weight (see Section 2.3.1 of this review), CL/F=26+0.808*WT, 10 kg difference in body weight would only result in ~10 % difference in clearance. Factors other than body weight also contributed to apparent oral clearance difference between adult RA patients and healthy adults.

Safety Results: Rofecoxib appears to be generally well tolerated by RA patients as noted in this study. One patient discontinued the study due to reoccurrence of nephrolithiasis but this was considered to be probably not associated with treatment. The more frequently noted adverse experiences included nausea, headache and symptoms of allergies. Most were considered to be not associated with the treatment.

Summary: Rheumatoid arthritis (RA) patients were dosed to steady state with the therapeutically efficacious dose of rofecoxib 25 mg. The $AUC_{0-24\ hr}$ geometric mean with corresponding 90% CI was 6642.4 ng·hr/mL (3382.21, 13045.4). The C_{max} geometric mean with corresponding 90% CI was 496.6 ng/mL (252.1, 978.2). The CL/F geometric mean with corresponding 90% CI was 62.1 mL/min (52.98, 72.80).

Compared to historical PK data from healthy adults (P042 and P043), rofecoxib showed lower clearance in RA patients with mean $AUC_{0-24\ hr}$ increased 46% and C_{max} increased 38%, respectively. Because CL/F of rofecoxib increases with body weight, weight difference may contribute to lower apparent oral clearance of rofecoxib in RA patients from this study than clearance in historical healthy adults in addition to disease and medical history factors.

PK dataset for adult RA patients for this study was limited (N=12) and does not fully reflect the demographics of the RA population in the pivotal clinical trials for Vioxx. Because of lower body weights of 12 PK patients than the RA population in the clinical trial, the exposure obtained from this study may be higher than the PK exposures (AUC) in the general RA population. However, 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 (generally weigh more and younger than RA patients) will be used for comparison to PK Data in JRA patients to provide additional information on pharmacokinetic behavior of rofecoxib in adults.

Rofecoxib 25 mg administered once daily for 10 days to RA patients is generally well tolerated.

4.2.2 JRA Patients (12-17 yrs) (Protocol 105, Part I)

An Open, Oral Dose Study to Evaluate the Steady-State Plasma Concentration Profile of Rofecoxib, Followed by a 12-Week, Double-Blind, Active-Comparator-Controlled Extension in Late-Stage and Postpubertal Adolescents With Juvenile Rheumatoid Arthritis (Protocol 105)

Study Period (Clinical Portion): August 9, 1999 to April 3, 2000

Principle Investigators and Study Centers:

Investigator Name and Address	Study Number	Number of Patients Enrolled
Richard Vehe, MD Department of Pediatrics, University of Minnesota 420 Delaware St. S.E., Box 817 Minneapolis, MN 55455-0392	105-002	5
Alan Kivitz, MD 711 Logan Boulevard Altoona, Pa 16602	105-003	4
Norman Ilowite, MD Pediatric Rheumatology, Schneider Childrens Hospital New Hyde Park, NY 11042	105-004	2

Analytical Site: Drug Metabolism Department, Merck & Co., Inc., West Point, PA 19486

(Reviewer's Note: This study has two parts: Part I, PK; Part II, Safety and Efficacy. Only review for Part I that is relevant to Clinical Pharmacology and Biopharmaceutics was included in this review.)

Objectives:

(1) To evaluate the steady-state plasma profile of rofecoxib in adolescent juvenile rheumatoid arthritis (JRA) patients.
(2) To compare the steady-state plasma profile of rofecoxib 12.5 mg or 25 mg in adolescent JRA patients to data from healthy adults and adult RA patients dosed with 25 mg daily.
(3) To evaluate the safety and tolerability of oral doses of 12.5 mg or 25 mg rofecoxib in latestage and postpubertal adolescents with JRA.

(Reviewer's Note: For Objective 2, the study report in the submission only compared JRA patient data to healthy adult data because there was no adult RA patient PK data at the time of the study. The comparison to adult RA patient data were included in Appendix 2.7.2:1, Memo of "Effect of Age on Pharmacokinetic Parameters in JRA Patients and Adults, and Determination of Dosing Regimen for Rofecoxib" and in responses to FDA request during the review process.)

Study Design: This was a 2-part study. Part I was a 14-day, open, oral dose, single-period pharmacokinetic study to evaluate the steady-state pharmacokinetics of rofecoxib in late-stage or

postpubertal adolescents (12-17 years old) with pauci- or poly-articular course JRA. Rofecoxib 12.5 mg or 25 mg was dosed, dependent on the patient's weight, to best approximate 0.322 mg/kg. In the current study, eligible patients weighing 40 to 60 kg received 12.5 mg rofecoxib and patients weighing >60 kg received 25 mg rofecoxib once daily, after a 1-day nonsteroidal anti-inflammatory drug washout period. On Day 13, multiple blood draws were obtained predose and postdose. On Day 14, patients had a fasting trough blood sample drawn and were eligible to enter Part II. Patients who did not wish to participate in the continuation period underwent discontinuation and poststudy procedures.

In Part II, patients who completed Part I were eligible for reassignment, in a double-blind fashion (determined by original allocation number), to rofecoxib (80%) or naproxen (20%) for 12 weeks. Patients who received 12.5 mg in Part I continued the same treatment or were reassigned to 375 mg naproxen twice daily. Patients who received 25 mg in Part I continued the same treatment or were reassigned to 500 mg naproxen twice daily. Patients had follow-up assessments after 2, 4, 8, and 12 weeks of Part II therapy. At Part II visits, patients were clinically evaluated, and blood and urine samples were obtained for safety monitoring.

Subjects: Eleven subjects who carried a diagnosis of pauci (oligo)- or polyarticular JRA, without active systemic symptoms (for the 3 months prior to the study) were enrolled into this study (Tables 1 and 2). Three were males, and eight were females. All subjects were Caucasians. Subjects ranged in age from 13 to 17 years, with a mean of 15 years. The mean weight was 57.4 kg with a range of 37.7 to 79.7 kg, and the mean height was 164.8 cm with a range of 138 to 185 cm. All completed Part I of the study. Eight subjects completed the Part II of the study.

Table 1. Age Distribution of Subjects and Their Dosing Scheme (Part I of the Study).

Age	N	Weight	N	Rofexoxib Dose
13	1	40-60 kg	7	12.5 mg QD for 13 days
14	5	>60 kg	4	25 mg QD for 13 days
16	3	Patients < 40 kg were excluded.		
17	2			

Table 2. Baseline Patient Characteristics.

Allocation Number	Age	Gender	Race	Weight (kg)	Height (cm)
000001	14	F	white	42.3	153
000003	13	M	white	50.7	162
000004	14	F	white	49.5	165
000005	16	F	white	59.6	175
000006	16	F	white	54.4	167
000008	14	F	white	39	152
000009	16	F	white	59.6	166
000002	14	F	white	63.7	138
000007	17	F	white	80.5	178
000010	14	M	white	69.2	185
000011	17	M	white	69.7	172

Test Product Information: Rofecoxib 12.5 mg (MR-3475) and 25 mg (MR-3491) tablets

Selection of Doses in the Study: The anticipated mean weight of adolescent JRA patients entering this study was approximately 60 kg. Rofecoxib doses of 12.5 mg, for patients weighing from 40 kg to 60 kg, and 25 mg, for patients weighing >60 kg, were selected based on the AUC(0-24 hr) for 25 mg in the healthy adult historical controls, as described below.

From historical healthy adult data (mean weight 77.7 kg), steady-state AUC(0-24 hr) values were estimated using a linear regression model for patient weight (AUC(0-24 hr) = 9967 ng·hr/mL – [{67 ng·hr/mL kg} x {weight in kg}]). The calculated mg-per-kg dose needed to reach the healthy adult-control AUC(0-24 hr) for 25 mg (4731 ng·hr/mL) is 0.322. For a 60-kg patient, the dose to match 25 mg in the healthy adult historical controls is 19 mg; the matching dose for a 40-kg patient is 13 mg. Similar results were obtained with a log-scale-transformed analysis. Actual patient doses used available tablet sizes of 12.5 mg and 25 mg.

The targeted dose for naproxen was 15 mg/kg/day based on pediatric rheumatology practices for treating JRA patients.

Sample Collection for PK Measurement:
Day 13: Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hours postdose.

Sample Analysis: Plasma samples were assayed for rofecoxib concentrations by the Merck & Co., Inc., Drug Metabolism Department. Plasma samples were analyzed in accordance with protocol DM-406 B. The analytical method utilized solid-phase extraction in a 96-well format and reversed-phase HPLC. The drug and internal standard (L-755100) were detected by fluorescence after post-column photochemical conversion of the analytes to fluorescent products. The lower limit of quantification (LLOQ) for MK-0966 in plasma was 0.50 ng/mL. A concentration of rofecoxib greater than 15% below LOQ was reported as NQ. The detailed bioanalytical report is included in Reference P105, Appendix 2.1.

Pharmacokinetic and Statistical Analysis: In Part I, pharmacokinetic parameters AUC_{0-24}, C_{max}, T_{max}, and CL/F were calculated for each subject.

This study was one of a set in which the steady state pharmacokinetics of rofecoxib were examined in pediatric patients (<18 years old). For the younger patients (2 to 5 years old) the sparsity and the pattern of data in the available plasma profiles precluded use of direct methods for estimating pharmacokinetic parameters (such as trapezoidal method for AUC). Additionally, it limited the complexity of the pharmacokinetic model which could be used for these estimations. Accordingly, pharmacokinetic parameters in those studies were estimated by fitting a one-compartment model with first order absorption and elimination to the data. For consistency, the pharmacokinetic parameters in this study were also estimated by fitting a compartment model. Since sampling in this study was more extensive, a 2-compartment model was fit to the data to obtain model parameters. Individual AUC_{0-24} values were estimated from the fitted values. Values of C_{max} and T_{max} were estimated by inspection of the fitted curve. CL/F was calculated by dividing each individual's dose by the individual's AUC_{0-24}.

Data for adult RA patients were obtained from Study Protocol P228. Data for healthy adults were obtained by combining the data from the rofecoxib Steady-State Dose Proportionality Study (Protocol 042 [25-mg dose], 14 subjects), and the rofecoxib Dose Proportionality Formulation C Study (Protocol 043 [25-mg dose], 12 subjects).

The steady-state pharmacokinetic parameters of rofecoxib 12.5-mg daily oral dosing in adolescent JRA patients weighing 40-60 kg or 25 mg in adolescent JRA patients weighing >60 kg, were compared with the historical plasma-concentration profile from the adult RA patients and healthy adults, using a one way analysis of variance (ANOVA) model. The ANOVA model contained the single factor age group with one degree of freedom (adolescent and adult). A log transformation, as appropriate, was applied to the AUC_{0-24}, C_{max}, and CL/F data. A rank transformation was applied to the pharmacokinetic parameter T_{max}. A 90% confidence interval (CI) for the ratio of least-squares (LS) means (back transformed from the log scale) from the above ANOVA model between the adolescents and the adult control subjects was computed for AUC_{0-24} and C_{max}.

Pharmacokinetic Results:

Pharmacokinetics of Rofecoxib in Adolescent JRA Patients

Table 3 lists individual PK parameters of rofecoxib in adolescent JRA patients who received two different doses based on body weight. Apparent oral clearance was similar between the two dose groups regardless of doses given indicating that PK was linear (dose-proportional) in this dose range. For JRA patients weigh 40-60 kg, CL/F was 89 ± 27 mL/min (Mean ± SD, n=7). For JRA patients weigh >60 kg, CL/F was 83 ± 6 mL/min (Mean ± SD, n=4).

Table 3. Individual Pharmacokinetic Parameters of Rofecoxib Estimated From Concentrations in Plasma Observed at Steady State.

AN	Age	Weight (kg)	AUC (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	CL/F (mL/min)
000001	14	42.3	3654	271	3.8	57
000003	13	50.7	1650	105	1.4	126.2
000004	14	49.5	2843	175	4	73.3
000005	16	59.6	2174	158	1.9	95.8
000006	16	54.4	1723	192	0.8	120.9
000008*	14	39	3088	238	2.4	67.5
000009	16	59.6	2582	236	1	80.7
000002	14	63.7	5298	342	2.8	78.6
000007	17	80.5	5250	393	1.6	79.4
000010	14	69.2	4509	362	1.7	92.4
000011	17	69.7	5070	383	2.3	82.2

**Reviewer's Note:* *AN 8 met the exclusion criteria because weight < 40 kg. However, the Sponsor included data in PK analysis. Because exclusion of this data will not change the conclusion, data will not be re-analyzed to exclude data from this patient.*

Comparison of CL/F for Adolescent JRA Patients and Adult RA Patients and Healthy Adults:

Adult RA Patients:

Table 4. Summary Statistics for Rofecoxib CL/F (mL/min) in Adolescent JRA Patients and Its Geometric Mean Ratio (GMR) Versus Adult RA Patients.

Age Group	Dose	N	CL/F Adjusted Mean†	GMR†	90% CI†
12- to 17- years old (P105)	12.5 or 25 mg	11	84.5	1.35	(1.11, 1.64)
Adult RA Patients (P228)	25 mg	12	62.7		
†Back-transformed from the log scale.					

Healthy Adults:

Table 5. Summary Statistics for Rofecoxib CL/F (mL/min) in Adolescent JRA Patients and Its Geometric Mean Ratio (GMR) Versus Healthy Adults.

Age Group	N	Mean†	Median‡	Min, Max‡	Approx. Within-Subject CV§	Between-Group p-Value	GMR‖	90% CI About GMR
Patients 12 to 17 years	11	84.5	80.7	57.0, 126.2	27.81	0.378	0.91	(0.77, 1.08)
Healthy adults	26	92.4	89.1	49.8, 180.7				

† LS mean back-transformed from the log scale.
‡ Back-transformed from the log scale.
§ CV = RMSE on the log scale x 100.
‖ GMR represents the LS mean ratio between adolescent groups versus the healthy adult controls comprised of rofecoxib patients from Protocols 042 and 043.
CV = coefficient of variation.
GMR = geometric mean ratio.
RMSE = root mean square error.

Comparison of AUC(0-24) for Adolescent JRA Patients and Adult RA Patients and Healthy Adults:

Adult RA Patients:

Table 6. Summary Statistics for Rofecoxib AUC(0-24hr) (ng·hr/mL) in Adolescent JRA Patients and Its Geometric Mean Ratio (GMR) Versus Adult RA Patients.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
12- to 17- years old‡ (P105)	25 mg	11	4928.4	0.74	(0.58, 0.94)
Adult RA Patients (P228)	25 mg	12	6642.4		
†Back-transformed from the log scale. ‡ The AUC(0-24hr) for pediatric patients between the ages of 12- to 17-years old dosed at 12.5 mg tablet were dose-adjusted to 25 mg.					

Healthy Adults:

Table 7. Summary Statistics for Rofecoxib AUC(0-24hr) (ng·hr/mL) in Adolescent JRA Patients and Its Geometric Mean Ratio (GMR) Versus Healthy Adults.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
12- to 17- years old‡ (P105)	25 mg	11	4928.4	1.08	(0.89, 1.32)
Healthy Adults (P042 and P043)	25 mg	26	4543.4		

†Back-transformed from the log scale.
‡ The AUC(0-24hr) for pediatric patients between the ages of 12- to 17-years old dosed at 12.5 mg tablet were dose-adjusted to 25 mg.

Comparison of Cmax for Adolescent JRA Patients and Adult RA Patients and Healthy Adults:
Adult RA Patients:

Table 8. Summary Statistics for Rofecoxib C_{max} (ng/mL) in Adolescent JRA Patients and Its GMR Versus Adult RA Patients.

Age Group	Dose	N	Cmax Adjusted Mean†	GMR†	90% CI†
12- to 17- years old‡ (P105)	25 mg	11	374.4	0.75	(0.62, 0.92)
Adult RA Patients (P228)	25 mg	12	496.6		

†Back-transformed from the log scale.
‡ The Cmax for pediatric patients between the ages of 12- to 17-years old dosed at 12.5 mg tablet were dose-adjusted to 25 mg.

Healthy Adults:

Table 9. Summary Statistics for the Rofecoxib C_{max} (ng/mL) in Adolescents (Weight Categories 40-60 kg and >60 kg) and Healthy Adults.

Pharmacokinetic Parameter	Age Groups and Weight Category†	N	Mean‡	Median§	Min, Max§	GMR
Cmax	Adolescents ≤60 kg	7	189	192	105, 271	0.52
	Adolescents >60 kg	4	369	372	342, 393	1.02
	Healthy Adults	26	361	356	173, 651	

† Note that mean weights (± SD) in kilograms are 50 (8), 70 (7), and 78 (12) for adolescents ≤60 kg, adolescents >60 kg, and adults, respectively.
‡ Least-squares means back-transformed from the log scale.
§ Back-transformed from the log scale.

Safety Results: Rofecoxib at doses of 12.5 mg and 25 mg daily demonstrates a favorable safety profile and is well tolerated by adolescent patients for up to 14 weeks.

Summary: For the adolescent JRA patients (13-17 yrs) who received 25 mg rofecoxib (4 of 11 total), the geometric mean steady-state AUC (0-24 hr) was 5022 ng·hr/mL; for the adolescent patients who received 12.5 mg rofecoxib (7 of 11 total), the geometric mean steady-state AUC

(0-24 hr) was 2438 ng·hr/mL. Mean oral clearance was 84.5 mL/min for this age group. There was not apparent dependence of oral clearance on body weight in this age group, therefore, dosing need not be adjusted for body weight. Oral clearance in adolescent JRA patients is higher than that obtained in adult RA patients (62.7 mL/min, GMR 1.35 (90% CI: 1.11, 1.64)) and lower than that obtained in healthy adults (92.4 mL/min, GMR 0.91 (90% CI: 0.77, 1.08)).

The Sponsor proposed a fixed dose of 25 mg rofecoxib for this age group for efficacy studies based on the healthy adult PK data because at the time of clinical study there was no PK data in adult RA patients and the Sponsor made the 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 dose effective dose ranges in JRA and RA patients. The GMR of dose-adjusted AUC_{0-24} for adolescent JRA patients to that of healthy adults was 1.08, and to that of adult RA patients was 0.74. Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the outcomes from the pivotal efficacy trial (P134/135) suggested that the dose selection was appropriate.

4.2.3 JRA Patients (2-11 yrs) (Study 109c)

An Open, Oral Dose Study to Evaluate the Steady-State Plasma Concentration Profile of Rofecoxib in Juvenile Rheumatoid Arthritis Patients, Aged 2 Through 11 Years (Protocol 109/110 Part I or Protocol 109c)

Study Period (Clinical Portion): Dec 7, 1999 to Mar 26, 2000.

Principle Investigators:

Investigator Name and Address	Study Number	Number of Patients Enrolled
Richard Rennebohm Division of Pediatric Rheumatology Children's Hospital 700 Children's Drive Columbus, OH 43205	109-001	1
Richard Vehe, MD Department of Pediatrics, University of Minnesota 420 Delaware St. S.E., Box 817 Minneapolis, MN 55455-0392	109-002	6
Maria Kiss Rua Itapolis 1624 Pacaembu - Sao Paulo, Brazil 01245-000	110-001	6
Oystein Forre Holmboesgt. 6 A, 0357 Oslo Norway	110-002	5
Manuel Ferrandiz Paseo Del Prado MZ. C Lote 10 URB. Lomas de la Molina Vieja La Molina Peru	110-003	7

Study Centers: 5 study sites in the U.S., Norway, Peru and Brazil.

Analytical Site: Drug Metabolism Department, Merck & Co., Inc., West Point, PA 19486

Objectives:

(1) To evaluate the steady-state temporal plasma concentration profile of rofecoxib in juvenile rheumatoid arthritis (JRA) patients from 2 age groups: 6 to 11 year olds and 2 to 5 year olds.
(2) To compare the steady-state area under the concentration-time curve of weight adjusted rofecoxib doses in 6- to 11-year-old JRA patients to data from healthy adults and adult RA patients dosed with 25 mg daily.
(3) To compare the steady-state AUC of weight-adjusted rofecoxib doses in 2- to 5-year-old JRA patients to data from healthy adults and adult RA patients dosed with 25 mg daily.
(4) To evaluate the safety and tolerability of oral doses of a suspension formulation of rofecoxib in 2 to 11 year olds with JRA.
(5) To gain experience for designing future studies with clinical measurements for assessing JRA.

(<u>Reviewer's Note:</u> For Objective 2, the study report in the submission only compared JRA patient data to healthy adult data because there was no adult RA patient PK data at the time of

the study. The comparison to adult RA patient data were included in Appendix 2.7.2:1, Memo of "Effect of Age on Pharmacokinetic Parameters in JRA Patients and Adults, and Determination of Dosing Regimen for Rofecoxib" and in responses to FDA request during the review process.)

Study Design: This was a 14-day, open, oral dose, single-period pharmacokinetic study to evaluate the steady-state pharmacokinetics in 2- to 11-year-old patients with pauci- or poly-articular course JRA. Separate sets of allocation numbers were generated for 6- to 11-year-old and 2- to 5-year-old patients. Patients received daily study drug as outpatients on Days 1 to 12, and a monitored dose (at the clinical research center) on Day 13 with monitoring through Day 14. To accommodate patient and parent schedules, the protocol allowed an 8-to 14-day window for the outpatient daily dosing period. Rofecoxib doses were adjusted to approximate 0.322 mg/kg, based on a linear-regression model, to give an AUC(0-24 hr) estimated to match exposure of 25 mg daily in adult historical controls (mean weight of 77.7 kg).

All patients received daily rofecoxib doses in a suspension formulation. Daily dose to approximate 0.322 mg/kg: patients weighing 30 to 40 kg received 4 mL of a 2.5-mg/mL suspension (10 mg); patients weighing ≥20 kg and <30 kg received 3 mL of a 2.5-mg/mL suspension (7.5 mg); and patients weighing ≥10 kg and <20 kg received 2 mL of a 2.5-mg/mL suspension (5 mg) (Table 1).

On Day 13 or the day of the monitored dose, a predose and multiple postdose blood samples were obtained. Six to 11 year olds followed a single sampling schedule, and 2 to 5 year olds followed either 1 of 2 sampling schedules (with fewer time points than for the 6 to 11 year olds) (Table 1). The assignment of the sampling schedule for 2- to 5-year-old patients was done centrally. On Day 14, patients had a follow-up clinical assessment, and a fasting trough sample drawn (according to sampling schedule; 24 hours after the Day 13 dose).

This study enrolled both U.S. and multinational cohorts of patients under separate protocol numbers (Protocol 109 and Protocol 110, respectively). The use of 2 protocol numbers was for administrative purposes only. The study was designed as a single study.

Table 1. Age Distribution for Subjects who Completed the Study and their Dose and Sampling Scheme.

<table>
<tr><th>Age</th><th>N</th><th>PK Dosing</th><th>PK Sampling</th></tr>
<tr><td>2</td><td>1</td><td rowspan="11">10-20 kg 5 mg
20-30 kg 7.5 mg
30-40 kg 10 mg

Patients <10 kg or >40 kg were excluded.</td><td rowspan="11">2-5 years old (N=11)
Schedule A (N=5):
0, 1, 2, 7.5 and 18 hr post dose

Schedule B (N=6):
0, 3, 5, 12, and 24 hr post dose

6-11 years old (N=13)
0, 1, 2, 4, 6, 9, 12, 18, and 24 hr post dose</td></tr>
<tr><td>3</td><td>2</td></tr>
<tr><td>4</td><td>4</td></tr>
<tr><td>5</td><td>4</td></tr>
<tr><td>6</td><td>1</td></tr>
<tr><td>7</td><td>1</td></tr>
<tr><td>8</td><td>2</td></tr>
<tr><td>9</td><td>3</td></tr>
<tr><td>10</td><td>5</td></tr>
<tr><td>11</td><td>1</td></tr>
<tr><td colspan="2">Age 2-5 11
Age 6-11 13</td></tr>
</table>

Subjects: 26 subjects who carried a diagnosis of pauci (oligo)- or polyarticular JRA, without active systemic symptoms (for the 3 months prior to the study) were enrolled into this study (Table 2). Eight were boys and 18 were girls. At least 3 patients weighing 10 to 20 kg were targeted; patients weighing <10 kg (22 lbs) or >40 kg (88 lbs) were excluded. In addition, the study was to enroll at least 3 Tanner Stage 2 and 3 patients in the 6- to 11-year-old group. All other patients were Tanner Stage 1. Subjects ranged in age from 2 to 11 years, with a mean of 7 years. The mean weight was 23.4 kg with a range of 13 to 38.6 kg, and the mean height was 118.1 cm with a range of 86 to 146.5 cm. Fourteen subjects were Caucasians (54%), 11 were multiracial (42%) and 1 was Asian (4%). 25 received study medication, and 24 completed the study. Subjects 20 and 22 in Study Number 110002 discontinued due to reasons unrelated to adverse experiences. Of the completers, 11 were aged 2 to 5 years and 13 were aged 6 to 10 years.

Table 2. Demographics and Baseline Characteristics.

Study Number	AN	Gender	Age	Tanner Stage	Weight (kg)	Height (cm)	Race
Patients Aged 2 to 5 Years, Weighing Between 10 kg and 20 kg							
110003	11	F	2	1	13.00	86.00	multiracial
110001	1	F	3	1	14.50	94.50	white
110002	19	F	3	1	15.50	99.00	white
110001	5	F	4	1	15.00	105.00	white
110002	20	M	4	1	16.70	108.00	white
110003	8	M	4	1	17.15	103.00	white
109002	7	F	4	1	17.90	104.20	white
110001	2	M	4	1	18.90	106.00	multiracial
110002	21	M	5	1	15.70	105.00	white
110003	7	F	5	1	16.50	104.00	multiracial
Patients Aged 2 to 5 Years, Weighing 20 kg or More							
109001	1	F	5	1	20.00	109.00	multiracial
109002	5	F	5	1	20.70	Not recorded	white
Patients Aged 6 to 11 Years, Tanner Stage 1							
110003	9	M	6	1	20.20	109.00	multiracial
110003	12	M	8	1	22.50	124.00	multiracial
110001	6	F	7	1	23.30	125.00	multiracial
110002	24	M	10	1	29.90	139.50	white
110001	4	M	9	1	30.80	128.00	multiracial
109002	13	F	9	1	33.30	127.00	white
109002	8	F	9	1	38.60	130.50	white
Patients Aged 6 to 11 Years, Tanner Stage 2 or 3							
110003	29	F	10	2	22.50	119.00	multiracial
110002	22	F	10	2	24.80	134.00	white
110001	3	F	10	2	28.00	133.50	multiracial
110003	10	F	8	2	30.20	125.00	multiracial
110002	23	F	10	2	30.80	145.00	white
109002	14	F	11	2	36.80	146.50	asian
109002	6	F	10	3	35.24	144.00	white
Mean:							
Boys	N/A	N/A	6	N/A	21.48	115.30	N/A
Girls	N/A	N/A	7	N/A	24.26	119.50	N/A
Combined	N/A	N/A	7	N/A	23.40	118.10	N/A
Range:							
Boys	N/A	N/A	4 to 10	1 to 2	15.70 to 30.80	103.00 to 139.50	N/A
Girls	N/A	N/A	2 to 11	1 to 3	13.00 to 38.60	86.00 to 146.50	N/A
Combined	N/A	N/A	2 to 11	1 to 3	13.00 to 38.60	86.00 to 146.50	N/A
N/A = Not applicable.							

Test Product Information: Rofecoxib oral suspension (Formulation Number, MR-4092), 2.5 mg/mL (12.5 mg/5 mL).

Selection of Doses in the Study: Weight-adjusted rofecoxib doses were selected based on the AUC(0-24 hr) values for the 25-mg dose in adults. Protocol 070 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).

From historical healthy adult data (mean weight 77.7 kg), AUCs(0-24 hr) were estimated using a linear-regression model for patient weight (AUC[0-24 hr]=9967 ng·hr/mL – [{67 ng·hr/mL kg} x {weight in kg}]). The calculated mg/kg dose needed to reach the adult control AUC(0-24 hr) for 25 mg (4731 ng·hr/mL) was 0.322 mg/kg. Similar results were obtained with a log-scale transformed analysis. Dosing for this study was, therefore, based on an assumption of linear pharmacokinetics. However, at least in adults, the pharmacokinetics of rofecoxib are nonlinear below the clinical dose range (<10 mg), and show accelerated clearance of drug. How this phenomenon would influence the disposition of these low doses in children was unknown at the outset of this study.

Sample Collection for PK Measurement:
Visit 2 (after 8-14 days of once daily dosing):
Age 2-5 years old (N=11):
Schedule A (N=5): Predose, 1, 2, 7.5 and 18 hr post dose
Schedule B (N=6): Predose, 3, 5, 12, and 24 hr post dose

Age 6-11 years old (N=13):
Predose, 1, 2, 4, 6, 9, 12, 18, and 24 hr post dose

Sample Analysis: Plasma samples were assayed for rofecoxib concentrations by the Merck & Co., Inc., Drug Metabolism Department. Plasma samples were analyzed in accordance with protocol DM-406 B (More details were described in Sample Analysis section of Section 4.2.2 of this review). The lower limit of quantification (LLOQ) for MK-0966 in plasma was 0.50 ng/mL. The detailed bioanalytical report is included in Reference P109c, Appendix 2.1.

Pharmacokinetic and Statistical Analysis: The following pharmacokinetic parameters were calculated for each patient: AUC_{0-24}, C_{max}, T_{max}, and CL/F.

This study included subjects from whom only limited sampling could be obtained (2 to 5 years old). For these patients, the sparsity and the pattern of data in the available plasma profiles precluded use of direct methods for estimating pharmacokinetic parameters (such as trapezoidal method for AUC). Additionally, it limited the complexity of the pharmacokinetic model which could be used for these estimations. Accordingly, pharmacokinetic parameters in these subjects were estimated by fitting a one-compartment model with first order absorption and elimination to the data. For the older children (6 to 11 years old), the pharmacokinetic parameters in this study were also estimated by fitting a compartment model to maintain consistency. Since sampling in this study was more extensive, a 2-compartment model was fit to the data.

Individual AUC_{0-24} values were estimated from the fitted values. Values of C_{max} and T_{max} were estimated by inspection of the fitted curve. CL/F was calculated by dividing each individual's dose by the individual's AUC_{0-24}.

Data for adult RA patients were obtained from Study Protocol P228. Data for healthy adults were obtained by combining the data from the rofecoxib Steady-State Dose Proportionality Study (Protocol 042 [25-mg dose], 14 subjects), and the rofecoxib Dose Proportionality Formulation C Study (Protocol 043 [25-mg dose], 12 subjects).

A one-way analysis of variance (ANOVA) model was used to compare the steady-state pharmacokinetic parameters, AUC_{0-24}, C_{max}, T_{max}, and CL/F from the 6- to 11-year-old patients and with adult historical data (from rofecoxib Protocols 042, 043 and 228). A 90% confidence interval (CI) around the geometric least squares (LS) mean ratio (GMR) for pediatric versus adult historical controls was provided for the AUC_{0-24} and C_{max}. Similar analysis was conducted for the 2 to 5 year olds. For informational purposes, a similar procedure as above was used to analyze the 2 to 5 year olds without these pediatric outliers.

Pharmacokinetic Results:

Pharmacokinetics of Rofecoxib in JRA Patients (Age 2-11 Yrs)

Table 3. Individual Pharmacokinetic Parameters of Rofecoxib Estimated From Concentrations in Plasma Observed at Steady State.

AN	Protocol	$AUC_{(0-24\ hr)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hours)	CL/F (mL/min)
Ages 6 to 11					
6	109	2510	231	1.1	66.4
8	109	2579	135	4.4	64.6
13	109	3386	205	3.5	49.2
14	109	2270	176	2.1	73.4
3	110	2752	186	1.2	45.4
4	110	3061	237	0.8	54.4
6	110	3645	238	2.2	34.3
9	110	2859	215	3.0	43.7
10	110	3988	222	0.4	41.8
12	110	2608	182	4.1	47.9
23	110	2650	222	1.4	62.9
24	110	3822	300	1.2	32.7
29	110	2085	158	3.3	59.9

AN	Schedule	Protocol	$AUC_{(0-24\ hr)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hours)	CL/F (mL/min)
Ages 2 to 5						
1	A	109	7041	528	2.8	17.8
7	A	109	3314	281	0.9	25.1
2	A	110	1668	133	0.4	50.0
7	A	110	1759	105	2.9	47.4
21	A	110	2326	211	1.7	35.8
5	B	109	8078	501	0.0	15.5
1	B	110	2261	203	0.9	36.8
5	B	110	1795	132	3.4	46.4
8	B	110	1100	92	4.5	75.7
11	B	110	2174	296	0.6	38.3
19	B	110	2708	193	1.2	30.8

As of note, two girls (AN 1 and 5, aged 2-5 yrs) weighed 20 kg and 20.7 kg, respectively had substantially higher exposure than the rest of the 2-5 yr old group (ANs 1 and 5 with AUCs of

7041 nghr/mL and 8078 nghr/mL, respectively). Outliers of similar magnitude have also been seen among healthy elderly adult subjects.

Comparison of CL/F for JRA Patients (2-11 Yrs) and Adult RA Patients and Healthy Adults:
The least squares (LS) mean rofecoxib CL/F was 34.8, 50.6, 62.7 and 92.4 mL/min for 2- to 5-year-old JRA patients, 6- to 11-year-old JRA patients, adult RA patients and the adult control subjects, respectively (Tables 4 and 5). For the 2- to 5-year-old patients, the CL/F LS mean ratio in the pediatric patients versus adult RA patients and healthy adults were 0.55 and 0.38, respectively. For the 6- to11-year-old patients, the CL/F LS mean ratio in the pediatric patients versus the adult RA patients and healthy adults were 0.81 and 0.55, respectively.

Adult RA Patients:

Table 4. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients (2-5 Yrs and 6-11 Yrs) 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 (P109c)	~0.32 mg/kg	11	34.8	0.55	(0.42, 0.73)
6- to 11- years old (P109c)	~0.32 mg/kg	13	50.6	0.81	(0.67, 0.98)
Adult RA Patients (P228)	25 mg	12	62.7		
†Back-transformed from the log scale.					

Healthy Adults:

Table 5. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients (2-5 Yrs and 6-11 Yrs) and Their Geometric Mean Ratios Versus Healthy Adults.

Age Group	Dose	N	CL/F Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c)	~0.32 mg/kg	11	34.8	0.38	(0.40, 0.47)
6- to 11- years old (P109c)	~0.32 mg/kg	13	50.6	0.55	(0.47, 0.64)
Healthy Adults (P042 and P043)	25 mg	26	92.4		
†Back-transformed from the log scale.					

Comparison of AUC(0-24) for JRA Patients (2-11 Yrs) and Adult RA Patients and Healthy Adults:
For the 2- to 5-year-old age group, the AUC geometric mean ratio (GMR) for children compared with adult RA patients and healthy adults were 0.39 and 0.57, respectively (Tables 6 and 7). Of note were two 5-year-old girls with substantially higher AUCs compared with the other patients in the 2- to 5-year-old age group (ANs 1 and 5 with AUCs of 7041 nghr/mL and 8078 nghr/mL, respectively). The majority of patients in the 2- to 5-year-old group had lower exposure than indicated by the overall mean value calculated with all patients included (Table 3).

For the 6- to 11-year-old age group, the AUC GMR for children compared with adult RA patients and healthy adults were 0.43 and 0.64, respectively (Tables 6 and 7).

Adult RA Patients:

Table 6. Summary Statistics for Rofecoxib AUC(0-24hr) (ng·hr/mL) in JRA Patients (2-5 Yrs and 6-11 Yrs) and Their Geometric Mean Ratios Versus Adult RA Patients.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c)	~0.32 mg/kg	11	2580.7	0.39	(0.28, 0.54)
2- to 5- years old (P109c) without outliers	~0.32 mg/kg	9	2033	0.31	Not Calculated
6- to 11- years old (P109c)	~0.32 mg/kg	13	2885.0	0.43	(0.36, 0.52)
Adult RA Patients (P228)	25 mg	12	6642.4		
†Back-transformed from the log scale.					

Healthy Adults:

Table 7. Summary Statistics for Rofecoxib AUC(0-24hr) (ng·hr/mL) in JRA Patients (2-5 Yrs and 6-11 Yrs) and Their Geometric Mean Ratios Versus Healthy Adults.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c)	~0.32 mg/kg	11	2580.7	0.57	(0.44, 0.73)
2- to 5- years old (P109c) without outliers	~0.32 mg/kg	9	2033	0.45	(0.37, 0.54)
6- to 11- years old (P109c)	~0.32 mg/kg	13	2885.0	0.64	(0.54, 0.74)
Healthy Adults (P042 and P043)	25 mg	26	4543.4		
†Back-transformed from the log scale.					

Comparison of C_{max} for JRA Patients (2-11 yrs) and Adult RA Patients and Healthy Adults:

Adult RA Patients:

For the 2- to 5-year-old age group, the C_{max} geometric mean ratio (GMR) for children compared with adult RA patients and healthy adults were 0.42 and 0.58, respectively (Tables 8 and 9).

For the 6- to 11-year-old age group, the C_{max} GMR for children compared with adult RA patients and healthy adults were 0.41 and 0.57, respectively (Tables 8 and 9).

Table 8. Summary Statistics for Rofecoxib C_{max} (ng/mL) in JRA Patients (2-5 Yrs and 6-11 Yrs) and Their Geometric Mean Ratios Versus Adult RA Patients.

Age Group	Dose	N	Cmax Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c)	~0.32 mg/kg	11	207.6	0.42	(0.30, 0.58)
6- to 11- years old (P109c)	~0.32 mg/kg	13	204.3	0.41	(0.34, 0.49)
Adult RA Patients (P228)	25 mg	12	496.6		
†Back-transformed from the log scale.					

Healthy Adults:

Table 8. Summary Statistics for Rofecoxib C_{max} (ng/mL) in JRA Patients (2-5 Yrs and 6-11 Yrs) and Their Geometric Mean Ratios Versus Healthy Adults.

Age Group	Dose	N	Cmax Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c)	~0.32 mg/kg	11	207.6	0.58	(0.45, 0.74)
6- to 11- years old (P109c)	~0.32 mg/kg	13	204.3	0.57	(0.48, 0.67)
Healthy Adults (P042 and P043)	25 mg	26	360.9		
†Back-transformed from the log scale.					

Safety Results: Rofecoxib had a favorable safety profile and was generally well tolerated in patients aged 2 to 11 years, for approximately 2 weeks. No unexpected or concerning patterns of adverse experiences arose. Subjects 20 and 22 in Study Number 110002 discontinued due to reasons unrelated to adverse experiences.

Summary: The least squares mean rofecoxib CL/F was 34.8, 50.6, 62.7 and 92.4 mL/min for 2- to 5-year-old JRA patients, 6- to 11-year-old JRA patients, adult RA patients and the adult control subjects, respectively. The rofecoxib CL/F for these 2 pediatric groups was significantly different than for the adult control subjects ($p<0.001$). This difference in clearance was consistent with different body sizes between the 2 age groups and lead to different dosing requirements for the adult control subjects and pediatric patients.

For the 2- to 5-year-old age group, the AUC GMR for children compared with adult RA patients and healthy adults were 0.39 and 0.57, respectively. For the 6- to 11-year-old age group, the AUC GMR for children compared with adult RA patients and healthy adults were 0.43 and 0.64, respectively.

Based on the overall results from this study, JRA patients aged 2 to 11 years who received a rofecoxib dose of ~0.322 mg/kg/day were underdosed relative to adult RA patients or healthy adults receiving 25 mg. Except for the outliers, exposure in this study (especially in the 2 to 5 year olds) more closely matched dosing with 12.5 mg in adults. Assuming dose proportionality,

one would predict that a doubling of the ~0.322-mg/kg/day dose in younger children (i.e., a dose of 0.6 to 0.7 mg/kg) would come closer to the pharmacokinetic equivalent of 25 mg in adults.

Follow-up pharmacokinetic data in 2- to 5-year-old children needed to be obtained to demonstrate that a doubling of the 0.322-mg/kg dose approximates exposure of 25 mg in adults. This would confine dose proportionality in the group differing the most from adults, and in which outliers were seen. (See Section 4.2.4, P109c2 or Protocol 109/110 Part II, in which a higher dose, ~0.7 mg/kg, was studied in age 2-5 JRA patients).

4.2.4 JRA Patients (2-5 yrs) (Study 109c2)

An Open, Oral-Dose Study to Evaluate the Steady-State Plasma Concentration Profile of Rofecoxib in Juvenile Rheumatoid Arthritis Patients, Aged 2 Through 5 Years (Part II) (Protocol 109/110 Part II or Protocol 109c2)

Study Period (Clinical Portion): Oct 25, 2000 to Dec 7, 2000.

Principle Investigators:

Investigator Name and Address	Study Number	Number of Patients Enrolled
Richard Rennebohm Division of Pediatric Rheumatology Children's Hospital 700 Children's Drive Columbus, OH 43205	109-001	3
Maria Kiss Rua Itapolis 1624 Pacaembu - Sao Paulo, Brazil 01245-000	110-001	4
Manuel Ferrandiz Paseo Del Prado MZ. C Lote 10 URB. Lomas de la Molina Vieja La Molina Peru	110-003	5

Study Centers: Multicenter (3) study sites in the United States (U.S.), Peru, and Brazil.

Analytical Sites: Drug Metabolism Department, Merck & Co., Inc., West Point, PA 19486

Objectives:

(1) To confirm the steady-state, temporal, plasma-concentration profile of rofecoxib, documented in 2- to 5-year-old juvenile rheumatoid arthritis (JRA) patients during Part I of the study.
(2) To compare the steady-state area under the concentration-time curve $(AUC)_{0\text{-}24\ hr}$ of weight-adjusted rofecoxib doses in 2- to 5-year-old JRA patients to data from healthy adults and adult RA patients dosed with 25 mg daily.
(3) To further evaluate the safety and tolerability of oral doses of a suspension formulation of rofecoxib in 2- to 5-year-old patients with JRA.
(4) To gain experience for designing future studies with clinical measurements for assessing JRA.

(Reviewer's Note: For Objective 2, the study report in the submission only compared JRA patient data to healthy adult data because there was no adult RA patient PK data at the time of the study. The comparison to adult RA patient data were included in Appendix 2.7.2:1, Memo of "Effect of Age on Pharmacokinetic Parameters in JRA Patients and Adults, and Determination of Dosing Regimen for Rofecoxib" and in responses to FDA request during the review process.)

Study Design: This was a 14-day, open, oral-dose, single-period pharmacokinetic study to evaluate the steady-state pharmacokinetics of rofecoxib in 2- to 5-year-old children with pauci- or poly-articular course JRA. Sampling for rofecoxib plasma concentrations occurred after the Day 13 dose, following a 12-day outpatient daily-dosing period. (Per protocol, a window of 8 to 14 days of dosing was allowed for the outpatient period.) Rofecoxib doses approximated 0.7 mg/kg, based on Part I study results, and were estimated to result in similar exposure to 25 mg daily in healthy adult historical controls (mean weight of 77.7 kg).

The study enrolled patients weighing at least 10 kg; all received daily weight-adjusted rofecoxib doses in a suspension formulation. On Day 13 (or at Visit 2 following the outpatient dosing period), rofecoxib was dosed with water under fasing state at the clinical site. Predose and multiple postdose blood samples were obtained (out to 24 hours postdose), with patients following 1 of 2 sampling schedules. Each schedule was restricted to a total of 5 blood draws. Blood samples were drawn at 0, 1, 2, 7.5, and 18 hours in Sampling Schedule A, and at 0, 3, 5, 12, and 24 hours in Sampling Schedule B (Table 1). On Day 14, patients had a follow-up clinical assessment.

This study enrolled both U.S. and multinational cohorts of patients under separate protocol numbers (Protocols 109 and 110, respectively), with identical study designs. The use of 2 protocol numbers was for administrative purposes only. The study was designed as a single study.

Table 1. Age Distribution for Subjects who Completed the Study and their Dose and Sampling Scheme.

Age	N	PK Dosing	PK Sampling
2	0	0.7 mg/kg	Schedule A (N=4): 0, 1, 2, 7.5 and 18 hr post dose. Schedule B (N=6): 0, 3, 5, 12, and 24 hr post dose
3	7		
4	1		
5	2		
Age 2-3 7 Age 4-5 3 Patients < 10 kg were excluded.			

Subjects: Twelve JRA subjects the diagnosis of pauci (oligo)- or polyarticular JRA (without active systemic symptoms for 3 months prior to enrollment) were enrolled into this study (Table 2). Five were boys and 7 were girls. Patients weighing <10 kg were excluded. Subjects ranged in age from 3 to 5 years, with a mean of 3.6 years. The mean weight was 16.7 kg with a range of 13.3 to 22.6 kg, and the mean height was 103.8 cm with a range of 94.5 to 114.4 cm. Three subjects were Caucasians (25%) and 9 were multiracial (75%). Ten patients completed the study. Two girls (ANs 50 and 87) discontinued from therapy who withdrew consent (not related to adverse experiences). Of the completers, 4 were boys and 6 were girls.

Table 2. Demographics and Baseline Characteristics.

AN	Protocol Number	Gender	Age (years)	Tanner Stage	Weight (kg)	Height (cm)	Race
50	109	Girl	5	1	21.6	112.0	Multiracial
51	109	Girl	5	1	22.6	114.4	White
52	109	Girl	4	1	18.2	108.3	White
76	110	Girl	3	1	16.0	98.0	Multiracial
77	110	Boy	3	1	13.3	94.5	White
78	110	Boy	5	1	20.0	110.0	Multiracial
79	110	Boy	3	1	14.8	99.0	Multiracial
82	110	Boy	3	1	15.4	99.0	Multiracial
84	110	Girl	3	1	18.7	108.0	Multiracial
85	110	Girl	3	1	13.8	109.0	Multiracial
86	110	Boy	3	1	16.6	99.0	Multiracial
87	110	Girl	3	1	19.0	104.0	Multiracial
Mean:							
Boys	N/A	N/A	3.4	N/A	16.01	100.30	N/A
Girls	N/A	N/A	3.7	N/A	17.15	105.46	N/A
Combined	N/A	N/A	3.6	N/A	16.69	103.80	N/A
Range:							
Boys	N/A	N/A	3 to 5	1	13.3 to 20.0	94.5 to 110.0	N/A
Girls	N/A	N/A	3 to 5	1	13.8 to 22.6	98.0 to 114.4	N/A
Combined	N/A	N/A	3 to 5	1	13.3 to 22.6	94.5 to 114.4	N/A
N/A = Not Applicable.							

Test Product Information:

Protocol No. /Country	Study Medication	Potency	Formulation No.	Dosage Form	Control No.	Clinical Batch No.
109/U.S.	Rofecoxib	5 mg/mL	4330	Oral suspension	CA-A938	9734
110/Brazil and Peru	Rofecoxib	5 mg/mL	4330	Oral suspension	CA-A943	9735

0.14 mL/kg (0.7 mg/kg) of rofecoxib oral suspension was dosed once daily to patients.

Selection of Doses in the Study: Weight adjusted rofecoxib doses were selected based on the observed AUCs0-24 hr for 25 mg in healthy adults (P042 and P043), 12.5 mg and 25 mg in adolescents (aged 12 to 17 years old (P105), and a 0.3-mg/kg approximated dose in children (aged 2 to 11 years old from Part I) (P109c). As shown in Protocol 109/110 Part I, in children aged 2 to 11 years given oral suspension, a dosing regimen targeted to 0.322 mg/kg/day yielded approximately half the systemic exposure of the 25-mg tablet (GMR of 0.60 compared with adults given 25 mg) and, thus, more closely approximated a 12.5-mg dose in adults.
Assuming dose proportionality, and excluding the outliers in Part I of the study, the calculated dose to match rofecoxib 25 mg in adults would be 0.6 to 0.7 mg/kg (for a 16.8-kg child; this was the mean weight for 2- to 5-year-old patients enrolled in Part I). Thus, 0.7 mg/kg was chosen as the dose for study in this confirmatory Part II study.

Sample Collection for PK Measurement:
Visit 2 (after 8-14 days of once daily dosing):
Schedule A (N=4): Predose, 1, 2, 7.5 and 18 hr post dose
Schedule B (N=6): Predose, 3, 5, 12, and 24 hr post dose

Sample Analysis: Plasma samples were assayed for rofecoxib concentrations by the Merck & Co., Inc., Drug Metabolism Department. Plasma samples were analyzed in accordance with protocol DM-406 B. (More details were described in Sample Analysis section of Section 4.2.2 of

this review). The lower limit of quantification (LLOQ) for MK-0966 in plasma was 0.50 ng/mL. The detailed bioanalytical report is included in Reference P109c2, Appendix 2.1.

Pharmacokinetic and Statistical Analysis: The following pharmacokinetic parameters were calculated for each patient: AUC_{0-24}, C_{max}, T_{max}, and CL/F.

This study included subjects from whom only limited sampling could be obtained (2 to 5 years old). For these patients, the sparsity and the pattern of data in the available plasma profiles precluded use of direct methods for estimating pharmacokinetic parameters (such as trapezoidal method for AUC). Additionally, it limited the complexity of the pharmacokinetic model which could be used for these estimations. Accordingly, pharmacokinetic parameters in these subjects were estimated by fitting a one-compartment model with first order absorption and elimination to the data.

Individual AUC_{0-24} values were estimated from the fitted values. Values of C_{max} and T_{max} were estimated by inspection of the fitted curve. CL/F was calculated by dividing each individual's dose by the individual's AUC_{0-24}.

Data for adult RA patients were obtained from Study Protocol P228. Data for healthy adults were obtained by combining the data from the rofecoxib Steady-State Dose Proportionality Study (Protocol 042 [25-mg dose], 14 subjects), and the rofecoxib Dose Proportionality Formulation C Study (Protocol 043 [25-mg dose], 12 subjects).

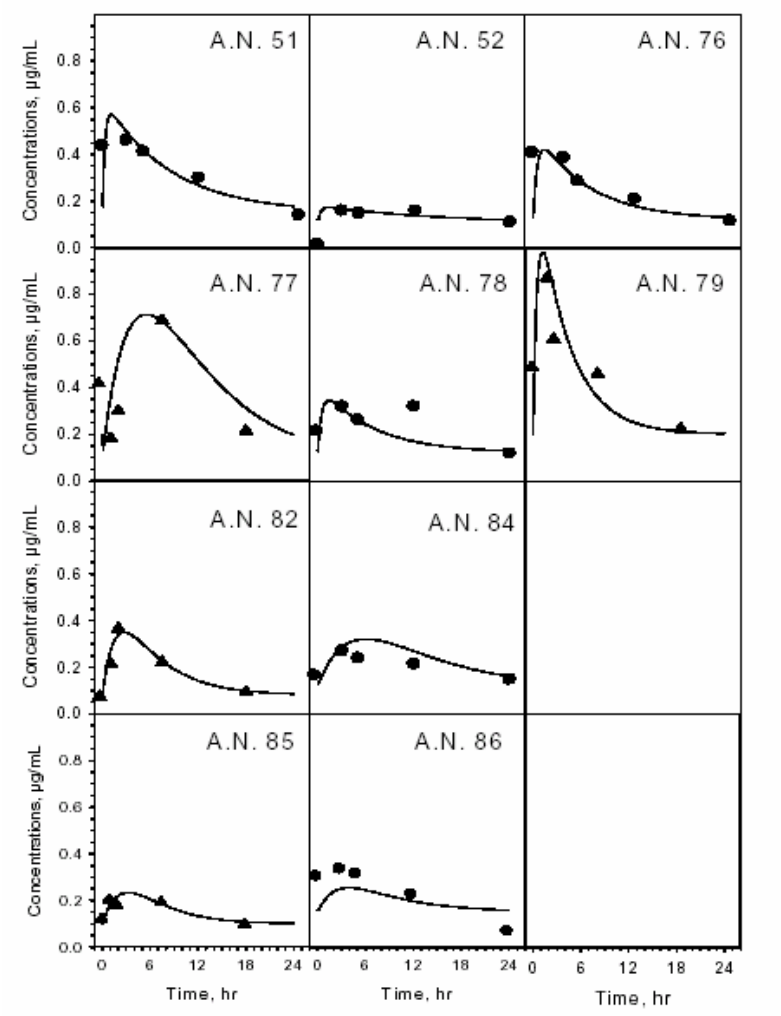
AUC_{0-24}, C_{max}, T_{max}, and CL/F from the 2- to 5-year-old patients and with adult historical data (from rofecoxib Protocols 042, 043, and 228). A 90% confidence interval (CI) around the geometric least squares (LS) mean ratio (GMR) for pediatric versus adult data (both RA and healthy) was provided for the AUC_{0-24} and C_{max}.

Pharmacokinetic Results:

Pharmacokinetics of Rofecoxib in JRA Patients (Age 2-5 Yrs)

Table 3. Individual Pharmacokinetic Parameters of Rofecoxib Estimated From Concentrations in Plasma Observed at Steady State.

AN	Schedule	Protocol	$AUC_{(0-24\ hr)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hours)	Cl/F (mL/min)
77	A	110	11010	713	5.6	15.1
79	A	110	8957	980	1.2	18.6
82	A	110	4215	349	2.7	43.5
85	A	110	4660	233	3.3	35.8
51	B	109	7344	570	1.1	36.3
52	B	109	3380	172	1.3	61.7
76	B	110	5258	420	1.4	31.7
78	B	110	4660	345	1.4	44.7
84	B	110	5876	321	6.1	36.9
86	B	110	4780	254	3.9	40.1



† ▲ Sampling Schedule A (0, 1, 2, 7.5, 18 hours).
• Sampling Schedule B (0, 3, 5, 12, 24 hours).

Figure 1. Estimated Steady-State Plasma Concentrations for Each Individual Pediatric Patient and Individual Best-Fit Curves†.

Comparison of CL/F for JRA Patients (2-5 yrs) and Adult RA Patients and Healthy Adults:
The least squares (LS) mean rofecoxib CL/F was 34.0 mL/min for 2- to 5-year-old JRA patients in this study. The CL/F LS mean ratio in this group of pediatric patients versus adult RA patients and healthy adults were 0.54 and 0.37, respectively (Tables 4 and 5). CL/F data obtained was similar to what have been obtained before for 2- to 5-year-old JRA patients receiving a lower rofecoxib dose of 0.32 mg/kg (34.8 mL/min) (See Review for Protocol 109c) indicating that PK is linear in this dose range for 2- to 5-year-old JRA patients.

Adult RA Patients:

Table 4. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Adult RA Patients.

Age Group	Dose	N	CL/F Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	34.0	0.54	(0.42, 0.71)
Adult RA Patients (P228)	25 mg	12	62.7		
†Back-transformed from the log scale.					

Healthy Adults:

Table 5. Summary Statistics for Rofecoxib CL/F (mL/min) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Healthy Adults.

Age Group	Dose	N	CL/F Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	34.0	0.37	(0.30, 0.46)
Healthy Adults (P042 and P043)	25 mg	26	92.4		
†Back-transformed from the log scale.					

Comparison of AUC(0-24) for JRA Patients (2-5 Yrs) and Adult RA Patients and Healthy Adults:

The AUC(0-24) GMR at steady state for children JRA patients (at a dose of 0.7 mg/kg QD) compared with adult RA patients and healthy adults (at a dose of 25 mg QD) were 0.85 and 1.24, respectively (Tables 6 and 7)

Adult RA Patients:

Table 6. Summary Statistics for Rofecoxib AUC(0-24 hr) (ng·hr/mL) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Adult RA Patients.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	5649.0	0.85	(0.66, 1.09)
Adult RA Patients (P228)	25 mg	12	6642.4		
†Back-transformed from the log scale.					

Healthy Adults:

Table 7. Summary Statistics for Rofecoxib AUC(0-24 hr) (ng·hr/mL) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Healthy Adults.

Age Group	Dose	N	AUC(0-24) Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	5649.0	1.24	(1.02, 1.51)
Healthy Adults (P042 and P043)	25 mg	26	4543.4		
†Back-transformed from the log scale.					

Comparison of C_{max} for JRA Patients (2-5 Yrs) and Adult RA Patients and Healthy Adults:

The C_{max} GMR at steady state for children JRA patients (at a dose of 0.7 mg/kg QD) compared with adult RA patients and healthy adults (at a dose of 25 mg QD) were 0.77 and 1.06, respectively.

Adult RA Patients:

Table 8. Summary Statistics for Rofecoxib C_{max} (ng/mL) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Adult RA Patients.

Age Group	Dose	N	Cmax Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	381.8	0.77	(0.56, 1.05)
Adult RA Patients (P228)	25 mg	12	496.6		
†Back-transformed from the log scale.					

Healthy Adults:

Table 9. Summary Statistics for Rofecoxib C_{max} (ng/mL) in JRA Patients (2-5 Yrs) and Its Geometric Mean Ratio (GMR) Versus Healthy Adults.

Age Group	Dose	N	Cmax Adjusted Mean†	GMR†	90% CI†
2- to 5- years old (P109c2)	~0.7 mg/kg	10	381.8	1.06	(0.83, 1.35)
Healthy Adults (P042 and P043)	25 mg	26	360.9		
†Back-transformed from the log scale.					

Safety Results: Rofecoxib, at a dose of ~0.7 mg/kg/day, had a favorable safety profile and was generally well tolerated in patients aged 2 to 5 years, for approximately 2 weeks. No serious or unexpected adverse experiences occurred. ANs 50 and 87, who discontinued form the study, reported no adverse experiences.

Summary: The least squares mean rofecoxib CL/F was 34.0 for 2- to 5-year old JRA patients receiving 0.7 mg/kg rofecoxib daily. CL/F data obtained in this study was similar to what have been obtained before for 2- to 5-year-old JRA patients receiving a lower rofecoxib dose of 0.32 mg/kg (34.8 mL/min) (P109c) indicating that PK is linear in this dose range for 2- to 5-year-old JRA patients. We could assume dose proportionality in this age group of JRA patients to adjust dose for comparable AUC to adults if needed.

The AUC GMR for JRA patients (2-5 yrs) compared with adult RA patients and healthy adults were 0.85 and 1.24, respectively. The C_{max} GMR for JRA patients (2-5 yrs) compared with adult RA patients and healthy adults were 0.77 and 1.06, respectively.

The study results confirmed that JRA patients aged 2 to 5 years who received a rofecoxib dose of ~0.7 mg/kg/day were dosed lower in terms of systemic exposure, relative to adult RA patients, and were dosed higher relative to adult historical controls who received 25 mg.

At the time of the study, no PK data was available in adult RA patients. The Sponsor assumed that RA patients would have similar clearance as healthy adults. Based on the study results, the Sponsor projected that 0.6 mg/kg/day in younger children would come closer to the systemic exposure equivalent of 25 mg dosed chronically in healthy adults because 90% CIs for the 0.6-mg/kg/day dose-adjusted AUC0-24 hr LS GMR of JRA patients (2-5 yrs) to healthy adults was (0.89, 1.32), reasonably approximated the exposure of 25 mg at steady state in healthy adults. Based on comparison to adult RA data (P228) that obtained later, a dose of 0.7 mg/kg or higher may be more optimal in terms of efficacy. However, the outcomes from the pivotal efficacy trial (P134/135) suggested that the dose selection was appropriate.

4.3 Pharmacometric (PM) Review

PHARMACOMETRIC REVIEW

NDA:	21-042/S026, NDA21-052/S019
Submission date:	December 5, 2003
Product:	12.5 and 25 mg tablet and suspension
Brand name:	VIOXX
Generic name:	rofecoxib
Sponsor:	Merck & Co., Inc.
Type of submission:	PM consult
Primary Reviewer:	Lei Zhang, Ph.D.
PM reviewer:	Jenny J Zheng, Ph.D.

Executive Summary:

The apparent clearance (CL/F) obtained from three pediatric studies (age ranged from 2-17 years old), one adult pharmacokinetic (PK) study in rheumatoid arthritis (RA) patients, and two adult PK studies in healthy subjects are pooled for the analysis of the effect of demographic factors such as age, body weight, body surface area, gender, and race on the CL of rofecoxib. The findings of the analysis are the followings:

- CL/F increases with age through adolescence. After adolescence, CL/F appears relatively unchanged with age, except for a suggestion that this parameter might decline somewhat with advancing age.
- CL/F increases with body weight. The relationship between CL/F vs weight can be described by a linear function, which suggests that the doses need to be given by body weight.
- Based on this analysis, a dose of 25 mg QD is proposed for adolescents (age from 12-17 years old) and a dose of 0.6 mg/kg is proposed for the pediatric patients less than 12 years old.
- The proposed doses were used in an efficacy trial. The efficacy assessment from the trial suggested the proposed doses are acceptable. Lower doses such as 12.5 mg for adolescents and 0.3 mg/kg for patients less than 12 years old were also used in the trial. (b) (4)

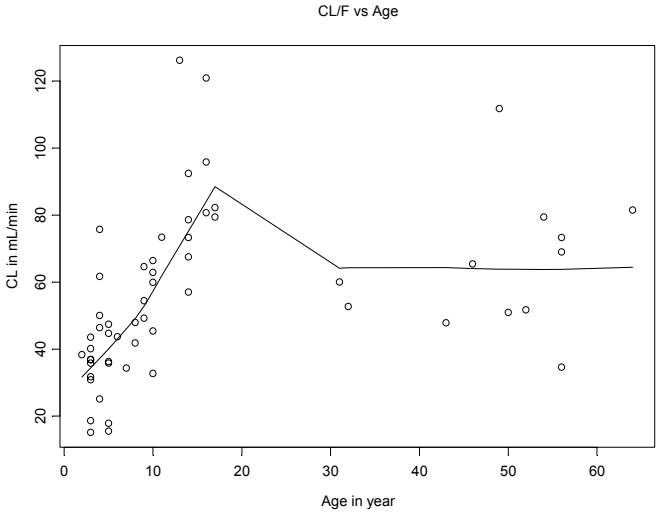
Methods:

The doses in pediatric patients were determined based on the comparison of PK between pediatric patients and healthy subjects when the PK data from adult RA patents were not available. The PK study in adult RA patients showed that the mean CL in RA patients is about 32% lower as compared with CL/F in healthy subjects (CL/F (mL/min): 62.7 vs. 92.4 mL/min). The sponsor's analysis showed that exposures in pediatric patients are comparable to the exposures in the pooled adult population including both healthy and RA patients. The exposures in pediatric subjects might be slightly lower as compared with the exposures in adult RA patients.

The relationship between CL/F vs age or body weight was explored by this reviewer after excluding the PK data from healthy subjects. The CL/F in pediatric patients and RA adult patients are shown in Figure 1. As shown in Figure 1, the CL/F increases as age increases in pediatric patients (up to 18 years old). The

CL/F in adult does not change much after 30 years old but the mean CL/F in adults appears lower than the CL/F in adolescents.

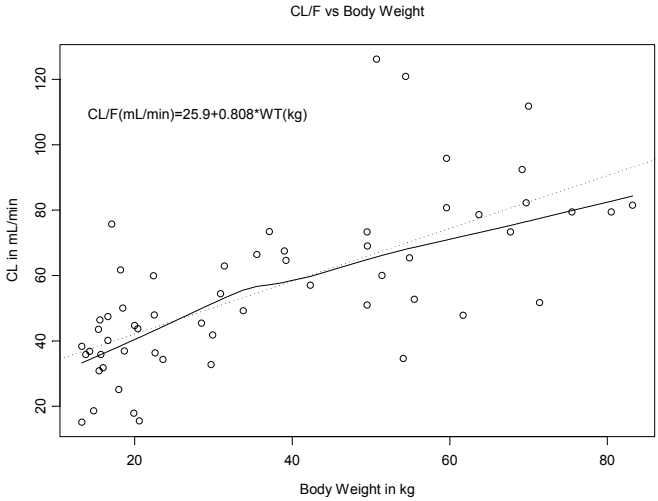
Figure 1.



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

The relationship between CL/F and body weight is presented in Figure 2. It shows that CL/F increases linearly as bodyweight increases, which suggest a body weight based dose should be appropriate.

Figure 2.

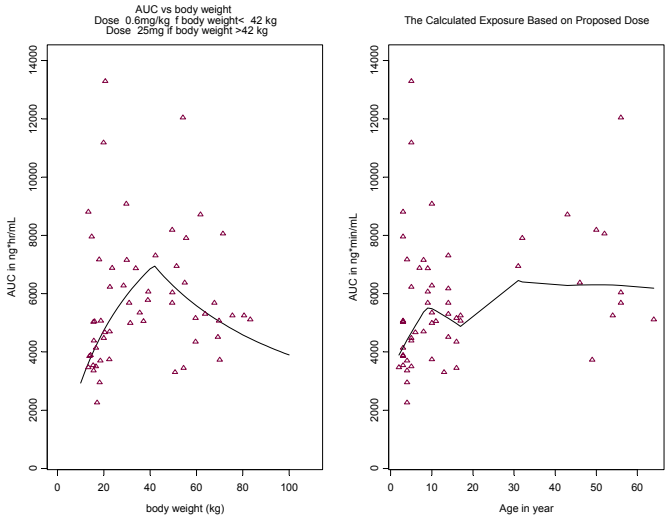


Dots represent the individual CL/F and the solid line represents the lowess regression line and the dash line represents the linear regression line

Based on proposed dose regimen by the sponsor, the exposures for the subjects in the studies were calculated and presented in Figure 3. Be aware that, the exposures shown in the left panel of the figure were calculated based on the relationship between CL/F and body weight. 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

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.

Figure 3.

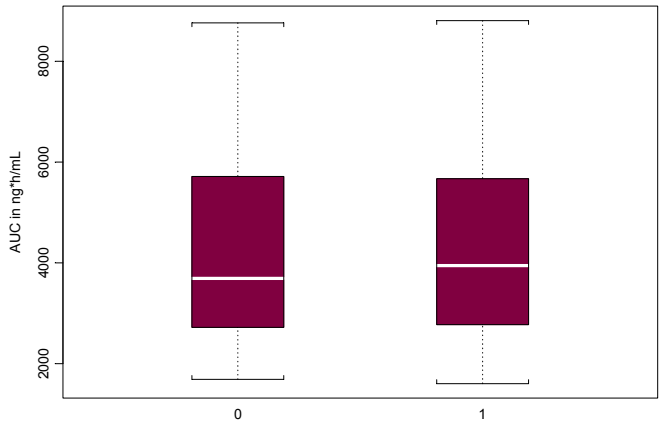


Left panel: Dots represent calculated individual AUC values for the subjects in the studies and the line represents the predicted mean exposure at different body weight at the dose of 0.6mg/kg.

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

Based on the relationship between CL/F and bodyweight and the dose, the exposures in the subjects recruited in efficacy study were calculated. It appears that the mean exposure is similar between responders and non-responders, indicating no apparent exposure response relationship was found (Figure 4).

Figure 4.



0 represents non-responder and 1 represents responder

RECOMMENDATIONS:
The analysis has been reviewed and the proposed doses in pediatric patients are found acceptable.

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Effect of Age on Pharmacokinetic Parameters in JRA Patients and Adults, and Determination of Dosing Regimen for Rofecoxib

Three pharmacokinetic (PK) studies in pediatric patients (Study 105, Study 109/110 Part I and Study 109/110 Part II, age ranged from 2 -17 years old), and one PK study in adult rheumatoid arthritis patients (Study 228, age ranged from 21-65 years old), were submitted in this application to support the use of Vioxx tablet/suspension for treatment of juvenile rheumatoid arthritis. In addition, an efficacy study was also conducted. PK data in healthy subjects from previous studies (Study 42 and Study 43) were used to compare the PK of rofecoxib between pediatric patients and adults. Please refer to Dr. Lei Zhang's review for the details of study designs of those studies.

The demographics of the pooled data from the five studies are shown in Table 1.

The apparent clearance (CL/F) obtained from those studies are pooled for the analysis of the effect of demographic factors such as age, body weight, body surface area, gender, and race on the CL/F of rofecoxib. The CL/F rather than exposure parameter such as area under the curve (AUC) was used in this analysis because various doses were given to the subjects in the studies. It is believed that PK of the drug is linear in the studied dose range so that the CL/F would not change across the studied doses.

Figure 1A shows CL/F by age for all subjects and patients in the PK studies. The relationship between CL/F and age is apparently continuous but not linear. Examination of the data in this figure suggests that CL/F increases with age through adolescence. After adolescence, CL/F appears relatively unchanged with age. The minimal effect of age on CL/F from age 12 is confirmed by the slope of the regression line for CL/F versus age for pooled adolescents and adults showed a slope not significantly different from zero (p=0.401) (Figure 1B). To understand the effect of age on PK in pediatric patients, the CL/F versus age was plotted across the pediatric age range (including the adolescent group) in Figure 1C. In patients aged 2 to 11 years, in contrast to the findings for subjects older than 11 years, CL/F increases with age, yielding a linear approximation with a slope significantly different from zero (p-value = 0.002). This finding is confirmed by the mean CL/F in the different age groups dosed in the rofecoxib PK studies (Table 2).

To examine if either of these two demographics provides predictive value, the relationship between CL/F versus weight (Figure 2) and CL/F versus BSA (Figure 3) was examined. A reasonable relationship was demonstrated between CL/F and each of the two demographics. The corresponding linear regression was calculated for each comparison showing that the dependence of CL/F on the demographic is very similar for both (adjusted $R^2 = 0.6036$ for weight and adjusted $R^2 = 0.5788$ for BSA).

Based on these analyses, it is recommended that JRA patients 2- to 11-years old are dosed by either weight or BSA with equal confidence. Since weight provides a more practical and simple approach to dose adjust versus BSA, this demographic is used for dose adjustment of this pediatric population.

In a post hoc analysis, the AUC (0-24hr)s were adjusted to the recommended dose of 0.6 mg/kg suspension (capped at 25 mg) for pediatric patients less than 12 years old and a fixed tablet dose of 25 mg for adolescents, the pooled pediatric JRA AUC(0-24hr) geometric mean with corresponding 90% CI was 1.00 (0.88, 1.13) compared to the pooled adult population including both healthy and RA patients.

Comments:

The sponsor's analysis was focus on the PK comparison between pediatric patients and the adult population including both healthy and RA patients. It shows that the mean CL/F in RA patients is about 32% lower as compared with CL/F in healthy subjects. The analysis showed that exposures in pediatric patients are comparable to the exposures in the pooled population including both healthy and RA patients. The exposure would be slightly lower in pediatric patients at the proposed dose as compared with exposure in RA patients only. However, the efficacy study demonstrated that slightly lower exposure in pediatric patients had little clinical significance. Therefore, the proposed doses are acceptable.

Table 1. Summary Statistics for Demographics of Pediatric JRA Patients and the Adult Population

		Age (Years)				Weight (Kg)			BSA (m2)		Sex				Race		
Age Group	n	Mean	Median	Min,Max	Mean (SD)	Median	Min,Max	Mean (SD)	Median	Min,Max	Female	Male	Asian	Black	Hispanic	White	Multi-racial
2 to 5 years (P109C,P109C2)	21	4.0 (1.0)	4.0	2.0, 5.0	16.8 (2.4)	16.5	13.0, 20.7	0.69 (0.07)	0.69	0.54,0.84	8	13	0	0	0	10	11
6 to 11 years (P109C)	13	9.0 (1.4)	9.0	6.0, 11.0	29.4 (5.9)	30.2	20.2,38.6	1.04 (0.14)	1.05	0.77,1.25	9	4	1	0	0	5	7
12 to 17 years (P105)	11	15.0 (1.4)	14.0	13.0,17.0	57.4 (12.5)	58.5	37.7,79.7	1.62 (0.22)	1.61	1.28,1.98	8	3	0	0	0	11	0
Healthy Adults (P042, P043)	26	35.6 (8.4)	36.0	20.0,48.0	77.7 (12.5)	79.9	52.3,104.5	1.93 (0.19)	1.94	1.56,2.28	9	17	0	4	7	15	0
RA Adults (P228)	12	49.1 (9.8)	51.0	31.0,64.0	62.0 (11.3)	58.6	49.5,83.2	1.68 (0.14)	1.68	1.50,1.93	10	2	0	0	0	12	0

Table 2. Summary Statistics for CL/F (mL/min) Following Administration of Rofecoxib to Different Age Groups

	N	**Adjusted Mean**[†]	**GMR**[†,‡]	**90% CI**[†] **of GMR**	
Age Group					
Combined 2 to 5 years old	21	34.4	0.42	(0.35,	0.50)
2 to 5 years old (Part I)	11	34.8	0.43	(0.34,	0.53)
2 to 5 years old (Part II)	10	34.0	0.42	(0.34,	0.52)
6 to 11 years old	13	50.6	0.62	(0.52,	0.74)
12 to 17 years old	11	84.5	1.03	(0.86,	1.25)
Pooled Adults[§]	38	81.8			

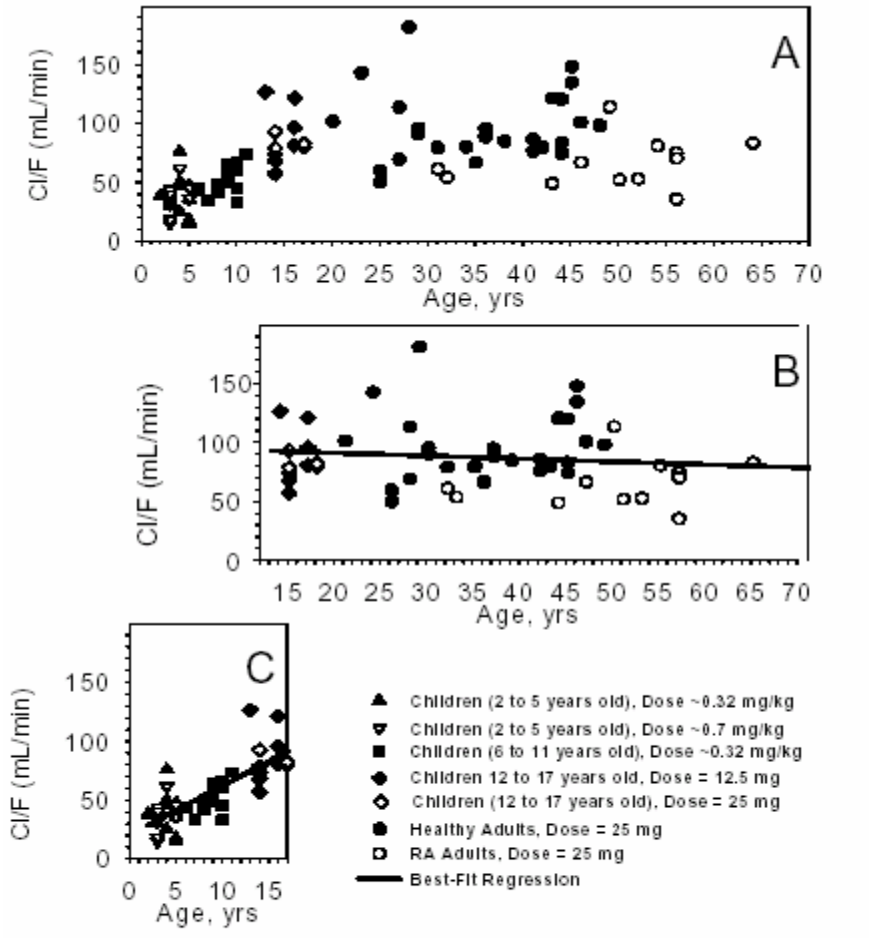
[†]Back-transformed from the log scale.
[‡] GMR of JRA patient age versus pooled adults.
[§] Combined Healthy Subjects and Adult RA patients.

Table 3: Comparison of Dose-adjusted AUC(0-24hr) (ng·hr/mL) for Pediatric Patients to Adults Following Administration of Rofecoxib

Parameter	**Age Group**	**N**	**Geometric Mean**	**Median**	**Min and Max**		**GMR**	**90% CI**
Dose- adjusted AUC(0-24hr)†	Pediatric Patients	45	5102.2	5047.7	2263.8	13377	1.00	(0.88,1.13)
	Pooled Adults	38	5122.3	5135.6	2324.1	11934		

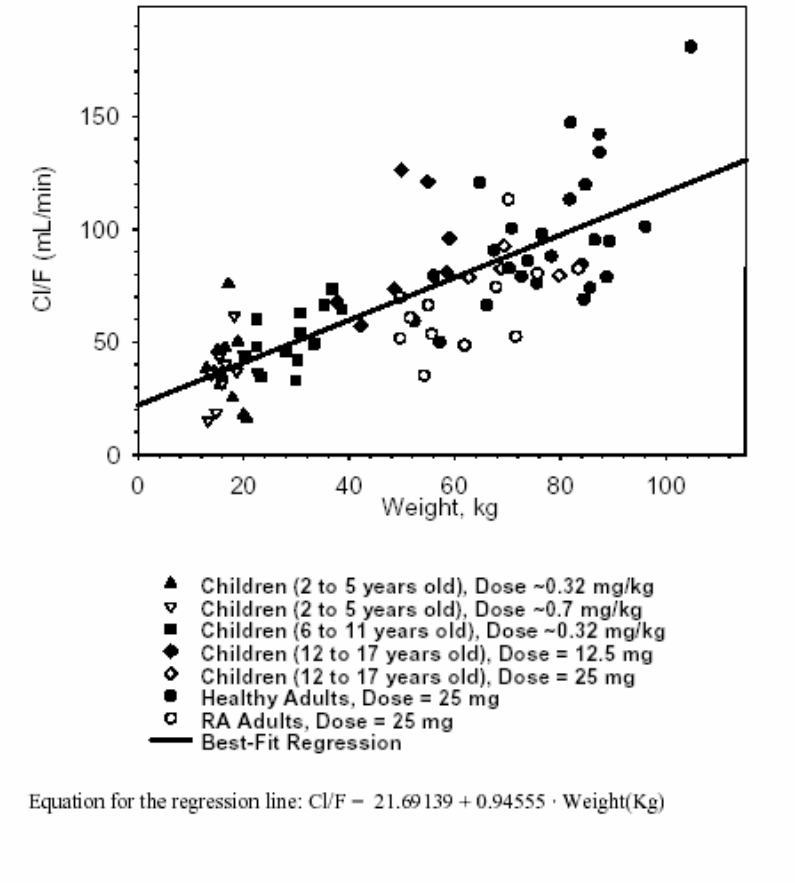
[†]Dosing regimen of 0.6 mg/kg (2 to 11 years; capped at 25 mg) with the adolescents receiving a fixed 25 mg dose.

Figure 1: Relationship Between CLearance/F (mL/min) and Age in JRA patients and Adults (A), in those Older than 12 years old (B), and Patients 2 to 17 years old (C). (Individual Values and Best Fit Regression Curves for Each Group are Depicted in Panels B and C)



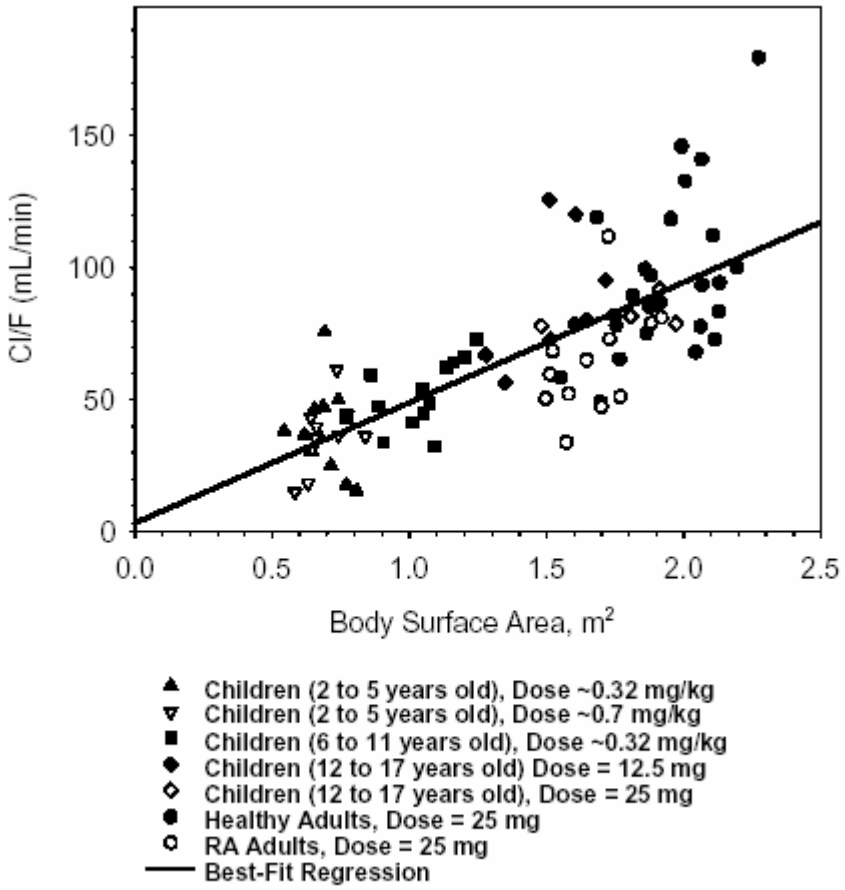
Equation for the Regression Line
B) Cl/F = 95.17374-0.247731 · Age (>11 years old)
C) Cl/F = 20.29463+4.15856 · Age (2-17 years old)

Figure 2: Relationship Between CL/F (mL/min) and Body Weight (Kg) in JRA Patients Aged 2 to 12 years, JRA patients Over 12, Healthy Adults Subjects and Adult RA Patients



Equation for the regression line: $Cl/F = 21.69139 + 0.94555 \cdot Weight(Kg)$

Figure 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



Equation for the regression line: Cl/F = 4.108256 + 45.61949 • Body Surface Area (m^2)

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/s/

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6/3/04 02:58:47 PM
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