U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-998 / S-021
Drug Name:	Celebrex ® (celecoxib capsules)
Indication(s):	Relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older
Applicant:	Pfizer, Inc.
Date(s):	Letter date: 6/20/06 PDUFA date: 12/14/06
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Clinical Team:	Medical Officer: Carolyn Yancey, M.D. Medical Team Leader: Rigoberto Roca, M.D.
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Keywords: Single clinical study; NDA review; Pediatric study

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Celebrex (celecoxib) is indicated for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis in adults, and ankylosing spondylitis. The drug is also indicated for the management of acute pain, the treatment of primary dysmenorrhea, and to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis. Pfizer currently proposes to add an indication for the relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older. The applicant has completed a single prospectively planned study in juvenile rheumatoid arthritis (JRA) patients to support the proposed indication.

The goal of the study was to assess the percent of patients achieving an improvement as measured by the JRA-30 score. The JRA-30 is based on six components, with success defined as at least 30% improvement on at least three components and no greater than 30% decrease in at most one of the components. The study was designed as a non-inferiority study, using 95% confidence intervals to compare each dose of celecoxib to the active-control naproxen group, with a pre-specified non-inferiority margin of -25%. Both the celecoxib 3mg/kg twice daily (BID) and 6mg/kg BID doses met the non-inferiority criterion.

In addition, the six components which compose the JRA-30 responder endpoint were analyzed as secondary endpoints. Pre-specified non-inferiority comparisons were not planned for these endpoints, and only descriptive statistics were provided. There were no notable differences for the components across the treatment groups.

The medical officer, Dr. Yancey, requested that I reanalyze the data excluding some patients who received higher doses under the protocol than would be allowed under the dosing regimen currently proposed by the applicant. Sixty-five patients (27%) of the total 242 were excluded from my reanalysis. The results did not change the overall conclusion.

In summary, my evaluation of the data derived from the JRA-30 showed that both doses of Celebrex met the pre-specified non-inferiority criterion. The additional secondary endpoints of interest to the Division of Anesthesia, Analgesia, and Rheumatology Products did not indicate any conflicting results. However, additional factors warrant consideration when assessing Celebrex for JRA patients. These factors include the unknown long-term effects of the treatment on children, the applicant's desire to market a different formulation of the drug than the one studied, and the limitations of the non-inferiority design in the proposed setting. Due to these factors, a definitive conclusion regarding the effect of the treatment is complicated and will require additional input from the Arthritis Advisory Committee.

1.2 Brief Overview of Clinical Studies

The applicant completed a prospectively planned, double-blind, randomized, active-control study to fulfill the requirements outlined in the pediatric written request issued on April 4, 2000 and revised on January 25, 2002. The study design is briefly outlined in Table 1. Pediatric patients were between 2 and 16 years old, and met entry criteria regarding swollen joints, joints with limited range of motion, and severity of illness assessed by physicians and parents. Patients were randomly assigned to receive one of the two celecoxib doses or naproxen during a 12-week double-blind treatment period. Some patients additionally

entered an optional 12-week open-label period. All patients received celecoxib at the highest proposed dose during the open-label period.

The primary endpoint was the percent of patients classified as responders based on the JRA-30 score at the end of the double-blind treatment period (Week 12). The JRA-30 endpoint included six separate components with success defined as improvement of at least 30% on at least three of the components, and no more than 30% worsening on at most one of the components. The six components of the JRA-30 responder outcome were analyzed as secondary endpoints.

The primary analysis was conducted on all randomized patients with at least one on-treatment measure. In the protocol, the applicant used a last observation carried forward (LOCF) imputation strategy for missing data prior to the Week 12 final efficacy visit. For the primary endpoint, each celecoxib group was compared to the naproxen group using a 2-sided 95% binomial confidence interval on the difference in the percent of responders. A non-inferiority margin of -25% was prespecified for these pairwise comparisons. No adjustments for multiple comparisons were made by the applicant. The components of the JRA-30 score were continuous variables, and were analyzed using analysis of covariance models with factors for treatment and site, and baseline value as the covariate. Non-inferiority margins were not predetermined for the secondary endpoints.

Table 1: Clinical Trial Description

Study (# of centers)	Design	Treatment groups (n)	Duration of treatment
N49-01-02-195 60 sites (US, Canada, Europe, South America)	Double-blind, Randomized, Active-control, Multicenter, Parallel arm	celecoxib 3mg/kg BID (n=77) celecoxib 6mg/kg BID (n=82) naproxen 7.5 mg/kg BID (n=83)	12 weeks double-blind phase, followed by an optional 12 week open-label with celecoxib 6 mg/kg BID treatment

1.3 Statistical Issues and Findings

During my review, I identified a potential statistical issue. The applicant used a LOCF strategy to handle missing data. This was planned in the protocol, and presented in the clinical report. My concern was that patients who demonstrated improvement but discontinued due to adverse events would possibly be counted as responders implying a treatment benefit. The concern would have been increased if a differential rate of dropouts among the treatment arms was evident. However, only a small percentage of patients withdrew from the study and the proportions of withdrawals were somewhat similar across treatment groups. In addition, the applicant performed an analysis whereby all dropouts were considered non-responders. The results of this analysis did not change the overall conclusions. Thus, my concern regarding missing data was alleviated.

Based on my evaluation of the submission, I find that both the celecoxib 3mg/kg BID and 6mg/kg BID

doses met the non-inferiority criterion, with lower bounds of the confidence intervals of -17 and -6, respectively (analysis considering all dropouts as non-responders). Moreover, the response rates at week 12 were 65%, 76%, and 68% in the celecoxib 3mg/kg, 6mg/kg, and naproxen treatment groups, respectively.

Conclusions regarding the effectiveness of the treatment are complicated by several factors. First, we cannot know the long-term effects of the treatment on children. Second, the applicant desires to market a different formulation of the drug than the one studied. Specifically, patients were administered an oral suspension formulation of the drug, but the proposed to-be-marketed formulation would be oral capsules. Lastly, the adequacy of the non-inferiority margin is difficult to assess due to the lack of placebo-controlled studies of naproxen using the JRA-30. In particular, JRA is a disease where improvement is common even among patients not receiving treatment. Thus, the margin should ideally be chosen utilizing information regarding the placebo response to diminish the likelihood of erroneous conclusions of efficacy resulting from similar responses between the treatment and placebo groups. In the absence of placebo-controlled studies, questions remain regarding the adequacy of the margin. Based on these factors, I cannot make a definitive statement regarding the effect of the treatment.

2. Introduction

2.1 Overview

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) approved for use in adults with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, primary dysmenorrhea, and familial adenomatous polyposis (FAP). The Celebrex label currently includes two black box warnings for the class of drugs. One warning states "Celebrex may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal." The other warns "NSAIDS, including Celebrex, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which could be fatal."

The applicant currently proposes to add an indication for the relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older. Juvenile rheumatoid arthritis (JRA) is a chronic disease which results in joint inflammation, pain, and stiffness. It can also lead to joint damage and changes in growth. It typically occurs from the toddler to early teenage years.

The applicant has submitted a double-blind, active-controlled study to support the proposed indication. The study was conducted in fulfillment of requirements outlined in the pediatric written request (PWR) issued on April 4, 2000 and revised on January 25, 2002. The following was outlined in the statistical information portion of the request:

> Three efficacy hypotheses should be formally tested – two equivalence (non-inferiority) tests, ruling out a clinically meaningful difference between each of the two celecoxib doses and the active control; and one difference test comparing the two celecoxib dosages used. Another option is to demonstrate superiority of celecoxib to the active comparator. Safety data should be analyzed by descriptive statistics.

In the revised request, the applicant was advised that the sample size should be large enough so that the study would "…be powered to rule out a clinically meaningful difference (prospectively defined) between at least one celecoxib dose and the active control (equivalence hypothesis) or to demonstrate that

celecoxib is superior to the active control." The applicant submitted the protocol on September 6, 2002, with a prespecified non-inferiority margin of -25%.

In addition, a pre-sNDA meeting between the sponsor and the Agency occurred on January 10, 2006. There were no statistical concerns discussed at the meeting.

My statistical review focuses on the single phase 3 study in juvenile rheumatoid arthritis patients submitted by the applicant. The study is referred to as Study 195.

2.2 Data Sources

All data was supplied by the applicant to the electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well. Additional data sets were provided as requested from the applicant. The data and final study report for the electronic submission were archived under the network path location \\Cdsesub1\n20998\S_0021\2006-06-20.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study N49-01-02-195 (conducted 10/02 to 4/05)

Design

Study 195 was a 12-week, randomized, double-blind, parallel arm, multicenter study. The objective was to evaluate the efficacy and safety of celecoxib suspension for the treatment of the signs and symptoms of JRA. It was an active-controlled study, with naproxen as the comparator treatment group. Naproxen was selected as the active comparator as it is generally accepted as a therapeutic option in the pediatric rheumatology community. After the 12-week double-blind treatment period, all patients had the option of continuing for a 12-week open-label period during which all patients received celecoxib at the 6 mg/kg BID dose.

An oral suspension formulation of celecoxib was administered at one of two dose levels: 3 mg/kg BID or 6 mg/kg BID. Naproxen was administered at 7.5 mg/kg BID. Although an oral suspension formulation was used in the study, the applicant requests consideration of an oral capsule containing 50 mg or 100 mg of celecoxib as the to-be-marketed formulation. The proposed doses of the capsules correspond to the 3 mg/kg and 6 mg/kg doses of the oral suspension formulation.

Patient Disposition

Patients were males and females, ages 2 to 16, weighing at least 9 kg. They had to meet minimum entry criteria regarding their JRA status, including at least one swollen joint and one joint with limited range of motion. In addition, the score based on the physicians' and parents' global assessments of disease severity had to be at least 10mm (on the 0-100 mm visual analog scale). The use of NSAIDs had to be discontinued prior to screening. However, patients could continue use of disease-modifying

antirheumatic drugs (DMARDs) provided a stable dosing regimen had been achieved prior to enrollment.

A total of 242 juvenile patients were enrolled in Study 195. Of these, 212 (88%) completed the 12-week double-blind treatment period. As shown in Table 2, the reasons for discontinuations were similar across the three treatment groups.

Table 2. Patient Disposition

	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
Randomized	n=77	n=82	n=83
Discontinued prior to Week 12:			
Total	10 (13%)	11 (13%)	9 (11%)
Reason:			
Adverse event	3 (4%)	7 (9%)	3 (4%)
Lack of efficacy	2 (3%)	1 (1%)	4 (5%)
Consent withdrawn	4 (5%)	2 (2%)	1 (1%)
Protocol violation	0 (0%)	1 (1%)	1 (1%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)
Completers	67 (87%)	71 (87%)	74 (89%)

Source: Clinical Study Report Table 13

Baseline Demographics

The three treatment groups were fairly balanced with respect to relevant demographic and baseline characteristics, as shown in Table 3.

Table 3. Patient Demographics for All Randomized Patients

	Celecoxib 3 mg/kg BID n=77	Celecoxib 6 mg/kg BID n=82	Naproxen 7.5 mg/kg BID n=83
Age (years)			
Mean (SD)	10.4 (4)	10.1 (4)	10.4 (4)
Age categories:			
2-5 yrs	14 (18%)	18 (22%)	11 (13%)
6-11 yrs	34 (44%)	30 (37%)	43 (52%)
12-16 yrs	29 (38%)	34 (41%)	29 (35%)
Gender			
Female	59 (77%)	53 (65%)	59 (71%)
Male	18 (23%)	29 (35%)	24 (29%)
Race			
White	41 (53%)	47 (57%)	52 (63%)
Black	9 (12%)	7 (9%)	4 (5%)
Asian	1 (1%)	3 (4%)	1 (1%)
Other/Not listed	26 (34%)	25 (30%)	26 (31%)
Weight			
Mean (SD)	36.2 (15)	36.2 (18)	37.3 (16)
Weight categories:			
≤ 12 kg	0 (0%)	2 (2%)	0 (0%)
Over 12 kg to ≤ 25 kg	21 (27%)	28 (34%)	22 (27%)
Over 25 kg to ≤ 50 kg	38 (49%)	35 (43%)	42 (51%)
Over 50 kg	18 (24%)	17 (21%)	19 (23%)
Type of JRA			
Pauciarticular	37 (48%)	45 (55%)	46 (55%)
Polyarticular	40 (52%)	37 (45%)	37 (45%)
Prior use of Methotrexate			
Yes	36 (47%)	33 (40%)	33 (40%)
No	41 (53%)	49 (60%)	50 (60%)

Sources: Clinical Study Report Tables 15 and 16; SAS datasets

Efficacy Results

The primary efficacy endpoint was the percent of responders on the JRA-30 scale. This endpoint was composed of six separate variables. A responder was defined as having at least 30% improvement on at least three of the six variables, and no more than 30% worsening on at most one of the remaining variables. Of the component variables, three were subjective questionnaire measures, two were joint counts, and the last component was a laboratory measure. The variables are listed in Table 4.

For the primary endpoint, each celecoxib group was compared to the naproxen group using a 95% 2-sided confidence interval on the difference in the percentage of responders. Changes from baseline to Week 12 in the six component variables of the JRA-30 were analyzed as secondary endpoints using an analysis of covariance (ANCOVA) model with terms for treatment, site, and baseline as the covariate. The results of the analyses of the secondary analyses are presented for exploratory purposes only, as there were no prespecified non-inferiority margins.

The applicant used a last observation carried forward (LOCF) strategy to impute missing data for the primary and secondary analyses. The primary analysis was conducted on the intent-to-treat (ITT) population included all randomized patients with at least one on-treatment measure. The results are presented in Table 4.

I was additionally interested in analyses whereby all dropouts were considered non-responders. I was concerned that patients who demonstrated improvement but discontinued due to adverse events would possibly be counted as responders implying a treatment benefit. My concern would have been increased if a differential rate of dropouts among the treatment arms was evident. However, only 12% of patients withdrew from the study, and the proportions of withdrawals were somewhat similar across treatment groups. The results of my analyses are shown in Table 5.

A comparison of Tables 4 and 5 shows that there were no notable differences between my analyses and those of the applicant. In both tables, the confidence intervals on the between-group differences did not exceed the non-inferiority margin for either celecoxib dose. The results for the six core components of the JRA-30 were also very similar in both tables. In the clinical study report, the applicant showed the percent of JRA-30 responders at Weeks 2, 4, and 8. At all timepoints, for both celecoxib groups, the lower bound of the 95% 2-sided confidence interval for the difference vs. naproxen did not exceed -25%. There was no prespecified non-inferiority criterion at these timepoints prior to Week 12.

Table 4. Applicant's Efficacy Results (ITT/LOCF)

	Celecoxib 3 mg/kg BID n=77	Celecoxib 6 mg/kg BID n=82	Naproxen 7.5 mg/kg BID n=83
Primary Efficacy:			
JRA-30 Responders at Week 12			
N (%)	53 (68.8%)	66 (80.5%)	56 (67.5%)
Difference vs. naproxen	+1.4%	+13.0%	
95% Confidence Interval	(-13.1%, 15.8%)	(-0.2%, 26.3%)	
Six Components of JRA-30:			
Physician's Global Assessment of Disease Activity (range 0-100)			
Baseline (SD)	42 (20)	41 (17)	41 (16)
Mean Change from Baseline (SD)	-22 (20)	-23 (19)	-22 (19)
Parent's Global Assessment of Overall Well-being (CHAQ Subsection) (range 0-100)			
Baseline (SD)	38 (22)	43 (20)	45 (23)
Mean Change from Baseline (SD)	-15 (27)	-21 (24)	-20 (27)
Functional Ability (CHAQ Disability Index) (range 0-3)			
Baseline (SD)	0.9 (0.6)	0.9 (0.6)	0.9 (0.7)
Mean Change from Baseline (SD)	-0.3 (0.5)	-0.3 (0.4)	-0.3 (0.6)
Number of Joints with Active Arthritis			
Baseline (SD)	8 (9)	7 (9)	6 (6)
Mean Change from Baseline (SD)	-2 (5)	-3 (6)	-3 (5)
Number of Joints with Limited Range of Motion			
Baseline (SD)	7 (9)	6 (8)	5 (5)
Mean Change from Baseline (SD)	-1 (5)	-3 (5)	-1 (3)
Laboratory Marker of Inflammation (C-Reactive Protein, mg/L)			
Baseline (SD)	12.3 (29)	14.9 (31)	16.9 (36)
Mean Change from Baseline (SD)	-2.4 (21)	-2.7 (25)	-1.1 (38)

Source: Clinical Study Report - Tables 19-25.

Table 5. Efficacy Results based on Non-responder Imputation (ITT)

	Celecoxib 3 mg/kg BID n=77	Celecoxib 6 mg/kg BID n=82	Naproxen 7.5 mg/kg BID n=83
Primary Efficacy:			
JRA-30 Responders at Week 12			
N (%)	50 (64.9%)	62 (75.6%)	56 (67.5%)
Difference vs. naproxen	-2.5%	+8.1%	
95% Confidence Interval	(-17.2%, 12.1%)	(-5.6%, 21.9%)	
Six Components of JRA-30:			
Week 12 Observed for Completers	n=67	n=71	n=74
Physician's Global Assessment of Disease Activity			
(range 0-100)			
Baseline (SD)	41 (19)	41 (18)	41 (16)
Mean Change from Baseline (SD)	-23 (21)	-25 (18)	-25 (16)
Parent's Global Assessment of Overall Well-being (CHAQ Subsection)			
(range 0-100)			
Baseline (SD)	37 (21)	42 (20)	44 (23)
Mean Change from Baseline (SD)	-18 (27)	-25 (22)	-23 (26)
Functional Ability (CHAQ Disability Index)			
(range 0-3)			
Baseline (SD)	0.9 (0.6)	0.9 (0.6)	0.9 (0.7)
Mean Change from Baseline (SD)	-0.3 (0.4)	-0.3 (0.4)	-0.4 (0.5)
Number of Joints with Active Arthritis			
Baseline (SD)	8 (9)	7 (9)	6 (6)
Mean Change from Baseline (SD)	-3 (5)	-4 (6)	-3 (5)
Number of Joints with Limited Range of Motion			
Baseline (SD)	6 (9)	7 (9)	5 (5)
Mean Change from Baseline (SD)	-1 (5)	-3 (5)	-2 (3)
Laboratory Marker of Inflammation (C-Reactive Protein, mg/L)			
Baseline (SD)	12.2 (30)	16.3 (33)	15.0 (34)
Mean Change from Baseline (SD)	-1.7 (22)	-4.1 (26)	-3.8 (29)

3.2 Evaluation of Safety

I provided the clinical reviewer, Dr. Yancey, with listings of adverse events separated according to the timing of adverse events during the double-blind or open-label periods. No additional assistance with the safety analyses was requested. Complete details on the adverse event profile are covered in Dr. Yancey's review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

The primary efficacy analyses were repeated for age groups, gender, and race. There were no notable differences in the responder rates for the treatments across any of these subgroups. This was seen in both my analyses (Table 6) and those of the applicant.

Table 6. Subgroup Results based on Non-responder Imputation (ITT)

Primary Endpoint: JRA-30 Responders at Week 12	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
Age categories: 2-5 years old 6-11 12-16	 11/14 (79%) 19/34 (56%) 20/29 (69%)	 14/18 (78%) 20/30 (67%) 28/34 (82%)	 7/11 (64%) 28/43 (65%) 21/29 (72%)
Gender Female Male	 38/59 (64%) 12/18 (67%)	 39/53 (74%) 23/29 (79%)	 41/59 (69%) 15/24 (63%)
Race Caucasian Non-Caucasian/Not listed	 27/41 (66%) 23/36 (64%)	 33/47 (70%) 29/35 (83%)	 35/52 (67%) 21/31 (68%)

4.2 Other Special/Subgroup Populations

Dr. Yancey requested a subgroup analysis which excluded patients who received higher doses of celecoxib under the protocol than would be allowed under the applicant's currently proposed dosing regimen. Only patients in the celecoxib treatment groups were administered doses higher than the proposed dosing regimen, reducing the number of patients in each of those groups. Even with the smaller samples sizes and classifying patients who discontinued as non-responders on the JRA-30 endpoint, both celecoxib doses levels met the non-inferiority margin of -25%.

Table 7. Subgroup Results based on Non-responder Imputation (ITT)

Primary Endpoint: JRA-30 Responders at Week 12	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
Patients Who Received Current Proposed Dosing (maximum 200 mg total per day)			
N (%)	38/59 (64%)	26/35 (74%)	56/83 (67%)
Difference vs. naproxen 95% Confidence Interval	-3% (-19%, 12%)	+7% (-11%, 24%)	

Dr. Yancey also requested additional subgroup analyses based on weight, prior use of methotrexate, and type of JRA, which is established by the number of joints affected. Pauciarticular JRA affects four or fewer joints. Polyarticular JRA affects five or more joints. These subgroup analyses are shown in Table 8. No notable differences in the treatment effect were evident among the subgroups.

Table 8. Subgroup Results based on Non-responder Imputation (ITT)

Primary Endpoint: JRA-30 Responders at Week 12	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
Weight categories: ≤ 12 kg Over 12 kg to ≤ 25 kg Over 25 kg to ≤ 50 kg Over 50 kg	 0 14/21 (67%) 25/38 (66%) 11/18 (61%)	 2/2 (100%) 20/28 (71%) 26/35 (74%) 14/17 (82%)	 0 16/22 (73%) 27/42 (64%) 13/19 (68%)
Type of JRA Pauciarticular Polyarticular	 26/37 (70%) 24/40 (60%)	 32/45 (71%) 30/37 (81%)	 35/46 (76%) 21/37 (57%)
Prior use of Methotrexate Yes No	 26/36 (72%) 24/41 (59%)	 24/33 (73%) 38/49 (78%)	 20/33 (61%) 36/50 (72%)

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The sponsor's planned analysis of the primary endpoint used a LOCF imputation strategy to handle missing data. I performed an analysis whereby patients with missing data were classified as non-responders. In an additional analysis requested by Dr. Yancey, patients who received a higher dose of celecoxib than allowed under the applicant's proposed dosing regimen were excluded, and patients with

missing data were classified as non-responders. In all the analyses, the proportion of responders was similar across the treatment groups, and both doses of celecoxib met the non-inferiority margin when compared to naproxen. However, the unknown long-term effects of the treatment on children, the applicant's desire to market a different formulation of the drug than the one studied, and the unknown adequacy of the non-inferiority margin in the absence of placebo-controlled trials of naproxen must all be considered when assessing the efficacy and safety of Celebrex for JRA patients.

5.2 Label Issues

The applicant's proposed label reports the results (b) (4)
I would recommend that the results using a non-responder imputation strategy be reported (see Table 5).

In the label, the sponsor states, (b) (4)
In my opinion, this statement in the label represents an additional claim and should be removed.

5.3 Conclusions and Recommendations

The results of the single study in this submission met the non-inferiority margin which was prespecified by the applicant. However, the adequacy of the margin is difficult to assess due to the lack of placebo-controlled studies of naproxen using the JRA-30. In particular, JRA is a disease where improvement is common even among patients not receiving treatment. Thus, the margin should ideally be chosen utilizing information regarding the placebo response to diminish the likelihood of erroneous conclusions of efficacy resulting from similar responses between the treatment and placebo groups. In the absence of placebo-controlled studies, questions remain regarding the adequacy of the margin and definitive statements regarding the effect of the treatment cannot be made without additional input from the Arthritis Advisory Committee on November 29, 2006.

In addition, other concerns arose during the review of the submission. The concerns include the unknown long-term effects of the treatment on children and the applicant's desire to market a different formulation of the drug than the one studied.

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