ADVISORY COMMITTEE MEETING

CELECOXIB FOR JUVENILE RHEUMATOID ARTHRITIS (NDA 20-998/S-021)

BRIEFING DOCUMENT

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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ABBREVIATIONS

ACR	American College of Rheumatology
ALT	alanine aminotransferase
ANA	antinuclear antibodies
APC	Prevention of Sporadic Colorectal Adenomas with Celecoxib [study]
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-X)	area under the concentration-time curve from time zero to x hours postdose
BID	twice daily
BPCA	Best Pharmaceuticals for Children Act
BRM	biological response modifier
BUN	blood urea nitrogen
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CEIFE	[Spanish Center for Pharmacoepidemiological Research] (translation)
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
Cmax	maximum plasma concentration
COX	cyclooxygenase
CRP	C-reactive protein
DAARP	Division of Anesthesia, Analgesia, and Rheumatology Products
DMARD	disease-modifying antirheumatic drug
DSMB	Data Safety Monitoring Board
EM	erythema multiforme
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
GI	gastrointestinal
GISSK	Gastrointestinal Symptom Scale for Kids
H_2RA	histamine-2 receptor antagonist
IA	intrarticular
ILAR	International League of Associations for Rheumatology
JRA	juvenile rheumatoid arthritis
JRA-30 DOI	JRA 30% Definition of Improvement
LDH	lactic dehydrogenase
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDA	New Drug Application
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
π_C	percent responders in the celecoxib treatment group
π_N	percent responders in the naproxen treatment group
PedsQL™	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PREA	Pediatric Research Equity Act
PRECISION	Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen [study]
PreSAP	Prevention of Colorectal Sporadic Adenomatous Polyps [study]
PRN	as needed
PWR	Pediatric Written Request
QD	daily
RA	rheumatoid arthritis
SCAR	severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
sNDA	Supplemental New Drug Application
TDD	total daily dose
TEN	toxic epidermal necrolysis
TNF	tumor necrosis factor
US	United States
VAS	visual analog scale

1. EXECUTIVE SUMMARY

This document summarizes the available data regarding the effects of celecoxib (a cyclooxygenase-2 [COX-2] selective non-steroidal anti-inflammatory drug [NSAID]) in treating the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA) in children over 2 years of age. CELEBREX® (celecoxib capsules) has been approved for use in, and proven efficacious in, treating the signs and symptoms of adult rheumatic conditions including osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis. In discussion with the Food and Drug Administration (FDA), the Sponsor undertook to study the use of celecoxib in treating the signs and symptoms of JRA in response to a Pediatric Written Request (PWR) that, when completed, would provide information to better inform appropriate labeling for the use of celecoxib in JRA. The work completed through the PWR was considered by the Sponsor to meet obligations set forth in the Pediatric Research Equity Act (PREA) as well as the agreed requirements for consideration of exclusivity under The Best Pharmaceuticals for Children Act (BPCA).

The PWR was comprised of a single study (Study N49-01-02-195, hereafter referred to as Study 195) assessing efficacy and safety of celecoxib in the JRA population and including pharmacokinetic assessments. In Study 195, celecoxib was shown to be safe and efficacious for use in JRA patients over 24 weeks of treatment. The first patient was enrolled in Study 195 in October 2002, and the last patient completed the study in April 2005.

Due to its selective inhibition of COX-2, celecoxib is an efficacious anti-inflammatory drug with less risk of gastrointestinal injury and bleeding as compared with nonselective inhibition of both COX-1 and COX-2 activity by traditional NSAIDs. CELEBREX has been granted marketing approval in the United States for the following indications in adults: relief of the signs and symptoms of OA, RA, and ankylosing spondylitis, and management of acute pain and primary dysmenorrhea. In oncology, CELEBREX has also been approved for the reduction of polyps in familial adenomatous polyposis (FAP) as an adjunct to usual care in adults.

As background, in late 2004 and early 2005, 2 selective COX-2 inhibitors (Bextra® [valdecoxib, Pfizer] and Vioxx® [rofecoxib, Merck]) were removed from the market due to safety concerns. In addition, in one of 2 long-term placebo-controlled chemoprevention trials, celecoxib was found to be associated with significantly increased cardiovascular risks. In 2005, FDA required all NSAIDs including CELEBREX to have the same boxed warning for cardiovascular safety. In addition, FDA determined that CELEBREX's benefits outweighed its risks for appropriate patients.

Further research has since become available increasingly solidifying the assessment that all NSAIDs have the potential to be associated with adverse cardiovascular outcomes independent of the degree of selectivity of COX-2 inhibition. These events were observed in adult populations and so warrant continued vigilance. While children have a very low risk of cardiovascular thromboembolic events, many children with JRA will enter adulthood with arthritis and may require NSAID therapy for prolonged periods.

This briefing document describes why there continues to be a medical need for NSAIDs for treating the signs and symptoms of JRA. Although relatively rare compared to adult arthritic

conditions, JRA represents an important chronic painful condition affecting up to 150 per 100,000 children at any time. Few NSAIDs are approved for treating JRA, and knowledge regarding adverse effects and long-term sequelae of treating children with NSAIDs is limited. Clinical Study 195 was conducted to compare celecoxib to naproxen in treating the signs and symptoms of JRA. This clinical trial demonstrated that celecoxib is non-inferior to naproxen with respect to efficacy, with a similar safety and tolerability profile. The clinical program for celecoxib was similar to those for other NSAIDs approved for JRA. None of these were sufficiently large, nor exposed patients for long durations of therapy to exclude rare or latent effects of treatment. Furthermore, Study 195 was designed in accordance with a PWR.

In the context of available data in both children and adults that suggest celecoxib's safety profile is similar to that of other nonselective NSAIDs, the benefit:risk profile of celecoxib appears favorable for use in JRA, as it is with other NSAIDs. There are, however, uncertainties related to long-term or latent effects with all NSAIDs which to date, studies cannot exclude. Children with JRA have a need for NSAID therapy, yet some NSAIDs are used in the absence of labeling.

Serious cardiovascular outcomes are extremely rare in childhood, and in general related to severe dyslipidemic or hypercoagulable states. Hypertension is, however, increasingly recognized as affecting around 4% of children and is second in prevalence only to obesity and asthma among chronic medical conditions in childhood. Both selective and nonselective NSAIDs may exacerbate underlying hypertension, which may be more pertinent than serious cardiovascular events in children. JRA and the need for NSAID therapy extend into young adulthood for approximately 40%-50% of patients. However, the latent effects of disturbing blood pressure control with NSAIDs in childhood are unknown. All available data, however, point to the conclusion that celecoxib has a similar profile for disturbance of blood pressure compared with other NSAIDs. The association in adulthood of hypertension and long-term cardiovascular morbidity and mortality is not disputed.

Compared to similar studies, including those with other NSAIDs, Study 195 is of similar magnitude and duration to exclude a certain level of risk. Available diagnosis data suggest that celecoxib is currently being prescribed to children with JRA in the absence of labeling. Therefore, it is important to provide physicians with information that may guide dosing and administration and relevant safety information needed to help protect patient safety.

In trying to balance the need for providing new therapies to patients with JRA and the potential for unknown risk, the Sponsor summarizes in this document the available data on the use of celecoxib in the pediatric population and the potential benefit to both prescribers and patients. The Sponsor puts forward this document to the Arthritis Advisory Committee, further to the supplemental new drug application (sNDA) currently under review by FDA, and requests consideration of various available labeling options, ranging from the inclusion of safety information and pharmacokinetic data, through to full approval of the indication to treat the symptoms of JRA. This request is made in the context of the BPCA, and in the interest of communicating important information to physicians prescribing celecoxib to treat JRA. Of great importance to the Sponsor is our ethical responsibility to make appropriate information available to guide prescribing decisions for children.

2. PRODUCT OVERVIEW

Celecoxib is a selective inhibitor of COX-2, the inducible form of the enzyme which catalyzes the formation of prostaglandins that act as proinflammatory mediators. As a result, celecoxib is an efficacious anti-inflammatory drug with less risk of gastrointestinal injury and bleeding as compared with nonselective inhibition of both COX-1 and COX-2 activity by traditional NSAIDs. CELEBREX was granted marketing approval in 1998 by the United States (US) Food and Drug Administration (FDA) (following review of New Drug Application [NDA] 20-998) for the relief of the signs and symptoms of osteoarthritis (OA), and for relief of the signs and symptoms of rheumatoid arthritis (RA) in adults. The recommended dose regimen for celecoxib is 200 mg daily in single (once daily [QD]) or divided (twice daily [BID]) doses in OA and 100 to 200 mg BID in adult RA. [1]

Following the marketing approval for OA and adult RA, celecoxib was granted approval in 2001 for the management of acute pain and primary dysmenorrhea in the US. The recommended dosing regimen of celecoxib for these conditions is 400 mg initially followed by an additional 200-mg dose if needed on the first day and 200 mg BID as needed (PRN) on subsequent days. In 2005, celecoxib was granted approval for the relief of signs and symptoms of ankylosing spondylitis in the US. The recommended dose of celecoxib for ankylosing spondylitis is 200 mg daily in single (QD) or divided (BID) doses, with dosing up to 400 mg daily if no effect is observed with the lower dose. In oncology, celecoxib 400 mg BID has been approved for the reduction of polyps in familial adenomatous polyposis (FAP) as an adjunct to usual care.

3. CHARACTERISTICS, EPIDEMIOLOGY, AND TREATMENT OF JRA

Juvenile rheumatoid arthritis (JRA) is a chronic painful inflammatory condition which often leads to joint dysfunction, destruction and deformity, with resultant disability.[2] Extra-articular features, such as uveitis in the pauciarticular subtype or fever, anemia, and pericarditis in the systemic subtype, may also cause significant morbidity. Thus, JRA may significantly impair the affected child's quality of life. JRA is considered a rare condition, but available studies have provided widely varying estimates of annual incidence and prevalence.[3,4,5,6,7] The more recent studies that utilized either national or hospital registries encompassing a full country's population or community-based methodology including examinations as well as surveys (which were included in a review of 34 epidemiological studies of juvenile arthritis published since 1966[6]) have shown that an annual incidence of 10-20/100,000 and prevalence of 50-150/100,000 children represent realistic estimates, though some feel these actually represent lower bounds due to continued under-recognition of pediatric arthritis by families and community practitioners. JRA is a disease in which the diagnosis is made clinically in a child "less than 16 years of age with arthritis (defined as swelling or limitation of motion of the joint accompanied by heat, pain, or tenderness) for at least 6 weeks duration with other identifiable causes of arthritis excluded."[7] The differential diagnosis of chronic arthritis in children is very broad and inclusive of many different diseases. Furthermore, laboratory tests and radiographs play a limited role in diagnosis; thus, the diagnosis of JRA is best made by a specialist with expertise in the evaluation of childhood arthritis. While JRA is considered a single disease, it most likely represents a

group of heterogeneous disorders of childhood sharing the predominant feature of idiopathic, chronic, inflammatory arthritis.

The treatment of JRA and its prognosis are guided initially by onset type, then on disease course, defined as the status of the disease at 6 months after initial diagnosis. Onset and course types have been defined by the American College of Rheumatology (ACR) and are divided into 3 categories (pauciarticular, polyarticular, and systemic), although more recently the nomenclature has been updated.[8] Since the ACR nomenclature was used throughout the development program for celecoxib in JRA, it is used in this document. Although the onset of JRA may occur at any age, clusters have been observed in children between the ages of 1 and 3 years for pauciarticular disease, and in older pre-adolescents for polyarticular disease. Systemic JRA can present at any age, and, in adults is often referred to as "adult-onset Still's disease." International League of Associations for Rheumatology (ILAR) classification uses the umbrella term Juvenile Idiopathic Arthritis instead of JRA. While diagnostic criteria are very similar, there are differences. For example, pauciarticular (renamed oligoarticular) and polyarticular disease are divided into subtypes, and 3 additional subtypes are included: psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis.

Pauciarticular JRA is the most common form of JRA, and its most common age of presentation is between the first and third years of life. Pauciarticular JRA predominantly affects girls, although older children and adolescents with pauciarticular disease are more likely to be boys and may represent early manifestations of a spondyloarthropathy. In the ILAR classification, this subtype is referred to as enthesitis-related arthritis, as patients often only have oligoarthritis and enthesitis at presentation or during the early course of disease, and not all will ever manifest to spondyloarthropathy such as ankylosing spondylitis. Systemic features like fatigue, malaise, and anorexia are typically minimal, and long-term prognosis is generally good. As many as two-thirds of children continue to have mild, stable disease or remitting disease; erosive arthritis is unusual. Nonetheless, complications are common. These include asymmetric bone growth (eg, leg length discrepancy with unilateral knee arthritis), which may lead to worsening of joint contracture and resultant abnormal gait, as well as subacute anterior uveitis. Anterior uveitis is more prevalent in younger, anti-nuclear antibody (ANA) sero-positive children (about 75% of pauciarticular patients) and may have a complicated course (which can include scarring or blindness) in about 20%.[9] Medication treatment of pauciarticular JRA most typically consists of intrarticular (IA) corticosteroid and NSAIDs. In fact, NSAID or IA corticosteroid alone can often remarkably decrease swelling and pain and facilitate normal function. Nonetheless, it is increasingly recognized that some pauciarticular patients will not respond to such therapies, and that disease-modifying antirheumatic drugs (DMARDs) or biological response modifiers (BRMs) may be necessary to suppress arthritis and/or uveitis. Also, at least 30% will have their disease evolve into a polyarticular course (referred to in the ILAR criteria as "extended oligoarticular" disease).[9] The prognosis of their disease is more guarded and similar to that of polyarticular disease; yet, they are still subject to uveitis.

Polyarticular JRA is the second most common form of JRA. Rheumatoid factor-negative polyarticular JRA typically presents around 6-7 years, while rheumatoid factor-positive disease (a relatively rare subtype analogous to adult RA) presents most commonly in children

aged 8-11 years, but also throughout adolescence. Polyarticular JRA most commonly affects girls, especially in the children who are older at onset. Systemic features like fatigue, malaise, and anorexia are common, and the prognosis is more guarded, with few children going into prolonged remissions and many children entering adulthood with arthritis. Complications include progressive, erosive arthritis with deformities as well as systemic manifestations such as vasculitic rash, rheumatoid nodules, subacute anterior uveitis and pulmonary disease. Pharmacological treatment of polyarticular JRA most typically consists of a regimen of DMARDs such as methotrexate or sulfasalazine. The anti-tumor necrosis factor-alpha (TNF-α) biological agent etanercept has also been approved for use in children, and is commonly used to further suppress disease activity. This has led to an improvement in overall outcomes of JRA. Nonetheless, many patients fail to completely respond to these therapies. Thus, most of the other biological agents that have been approved for adult RA (infliximab, adalimumab, abatacept, rituximab, anakinra) have also been or are currently being tested in clinical trials in JRA. Also, NSAIDs are still commonly used, and often on a regular basis, to control symptoms such as pain and stiffness, decrease inflammatory signs such as swelling, and facilitate improved function.

Systemic-onset JRA is the least common form of JRA, but can be very severe in its manifestations and challenging to treat. It affects boys and girls approximately equally, and has no predominant age of onset. Prognosis is variable. Some children have little arthritis and their systemic features remit. However, approximately 40%-50% have aggressive, recalcitrant erosive arthritis and/or intermittently debilitating or life-threatening systemic manifestations.[9] Presentation includes high spiking fevers, often with an evanescent salmon colored rash, and anemia. Pericarditis, pleuritis, and macrophage activation syndrome[10] (comprised primarily of disseminated intravascular coagulopathy, transaminase elevation, and altered mental status, accompanied by the bone marrow pathological findings of activated macrophages undergoing hemophagocytosis) may be present at onset or may complicate the course of the disease. Medication treatment depends on disease manifestations. Severe arthritis is treated with an aggressive DMARD/biological regimen. Systemic symptoms and arthritis are often treated with NSAIDs. Some patients, though, have such aggressive disease that experimental protocols have been utilized including therapies such as cyclophosphamide, cyclosporine A, intravenous immune globulin, and immune ablation followed by autologous stem cell transplantation.

Pain is a common and under-appreciated feature of all types of JRA. In a study of 293 children with JRA, 86% reported pain during a routine clinic visit.[11] The pain of JRA may be persistent. For example, in a study of 462 children with JRA, 60% reported joint pain at onset, 51% at 1-year follow-up, and 41% at 5-year follow-up.[12] Another study of 41 children used daily pain diaries to assess pain.[13] In this study, pain was reported on average 73% of days; 76% of children reported pain on more than 60% of days. It is notable that pain may be present despite treatment with disease modifying drugs considered highly efficacious; notably, in the pain-diary study 66% were receiving methotrexate and 17% were receiving etanercept. Indeed, the pain of JRA does not correlate well with disease activity, and pain may be present despite well-controlled arthritis.[13]

Much of JRA pain is mild to moderate in intensity; however, up to 25% of children report pain of "high intensity."[14] Higher levels of pain in children with chronic arthritis have been

associated with poor functional outcomes including reduction in school attendance and social activities.[14, 15, 16, 17] Pain intensity has been associated with daily activity impairment and healthcare utilization in children.[18] Walco et al[19] suggest that inadequate pain control in children is substandard and unethical medical practice. It is thus important to assess pain as well as assessing objective measures of arthritis activity in children with JRA, and to treat the pain of JRA adequately. Thus, even when other aggressive treatments are being used, or on the other extreme, when objective measures of disease activity are mild, NSAIDs are frequently used either acutely or chronically to treat signs and symptoms in children with JRA.

Although NSAIDs are used in a large majority of patients with JRA, few have been approved for this indication in the US (naproxen, ibuprofen, tolmetin, oxaprozin, and meloxicam). The only COX-2 selective inhibitor to have been approved for JRA (rofecoxib) was withdrawn from all markets worldwide in 2004. Meloxicam was approved afterwards in August 2005. Surveys of therapies prescribed by pediatric rheumatologists for JRA indicated that NSAIDs continue to be used for the treatment of the disease in approximately 80% of the cases of JRA.[20,21,22] NSAIDs can be particularly useful in children who do not require DMARD therapy or as an adjunct to DMARD treatment when pain persists or response is incomplete.[22] It is important to emphasize that NSAIDs are often the only therapy used by some JRA patients, and that even when it is used in additive fashion to an aggressive DMARD regimen, clinical responses may be quite robust. This has been illustrated in the recent clinical trials of meloxicam and rofecoxib.[23, 24]

The Sponsor has estimated the use of celecoxib in 2005 for children with arthritic conditions from market diagnosis/use data. This is based on data from a monthly survey of approximately 3,400 office-based physicians, representing 29 different specialties, across the United States. The survey captures each physician's diagnosis by ICD-9 code, age, and the subsequent drug prescribed. From these data, it is estimated in 2005 there were approximately 6,000 diagnosis episodes for JRA in those aged 18 years or less for which celecoxib was prescribed. This represents around 5%-6% of total NSAID use in JRA for this population. These data are, however, approximate and should only be used as directional indicators of current and previous exposure of the pediatric population to celecoxib. The data provide information only on patients seeking treatment, and measure physician intent; differences will exist when comparing these data to retail pharmaceutical volume data (eg, filled prescriptions).[25]

Overall, many children with JRA have a good prognosis, and advances in medical therapeutics such as methotrexate and etanercept have led to an even more improved outlook. However, many children still have severe and/or persistent disease that requires ongoing treatment. This treatment regimen most often includes NSAIDs for persistent signs and symptoms of arthritis.

4. PREDICTED AND KNOWN SAFETY PROFILES OF NSAIDs IN CHILDREN

While NSAIDs are widely used in JRA, some children tolerate them poorly and develop significant gastrointestinal (GI) symptoms, which are the most common types of adverse events reported with NSAIDs in the JRA population.[26,42] For example, a prospective study of

203 children with JRA found that 67% had documented GI symptoms at some stage during NSAID therapy. The most commonly reported GI symptoms were abdominal pain (50%) and appetite loss (32%).[27]

The extent of continued NSAID use into adulthood by people who have had JRA can be approximated by what is known about the degree of persistence of JRA into adulthood. It is estimated that approximately 40% to 50% of JRA patients have active arthritis at some point during adulthood, most often in those with a polyarticular course of their disease.[9] Also, even in patients in whom arthritis itself does not persist, persistent pain is a common problem. This may be multi-factorial, including pain from damage due to the previous JRA, a pain amplification syndrome (which often occurs secondarily in patients with rheumatic diseases), or an overt psychosomatic condition. Thus, it is likely that a significant proportion of children who had JRA will continue to use NSAIDs into adulthood.

4.1. Gastrointestinal Effects

Clinical trials in children with JRA have been conducted with a number of NSAIDs.[23, 24, 28, 29, 30, 31 , 32, 33, 34, 35, 36, 37, 38] Differences in study design, and the fact that many of these studies were conducted in an earlier era of medical treatment of JRA, make it difficult to compare results across studies; however, some inferences can be made. For instance, the most common adverse events are abdominal pain, nausea, vomiting, and diarrhea.

Many of these clinical trials were of short duration, with the longest exposure being 1 year, thus providing limited information on long-term use. A number of trials and observational studies have been conducted to determine the prevalence of GI complications of NSAID therapies over time and in a real-world clinical setting. Estimates of NSAID-associated gastropathy in patients with JRA range from 0.7% to 75%, depending on differences in study design.[26,39,40,41,42,43] The most comprehensive of these studies[42] followed 570 children in a pediatric rheumatology clinic, the large majority of whom had JRA, over a 3-year period. A total of 344 of these children used NSAIDs for a mean of 22.1 months. During this 3-year period, 49% of children on NSAIDs vs. 42% of those not on NSAIDs developed abdominal pain; however, 34% of those with abdominal pain on NSAIDs had radiographic or endoscopic evidence of gastroduodenal injury, while only 7% of those with abdominal pain without NSAID use had such evidence. After controlling for prednisone and DMARD use, this yielded a relative risk of 4.8 for gastroduodenal injury in JRA patients with abdominal pain in NSAID users vs. non-users. Recently, a tool (the Gastrointestinal Symptom Scale for Kids [GISSK]) has been developed and validated, which assesses dyspepsia symptoms in children with JRA.[44] A total of 81% of the patients in the validation study were on nonselective NSAIDs, while an additional 10% took COX-2 selective inhibitors. Despite the fact that 32% of these patients were taking concomitant GI-protective medications (primarily proton-pump inhibitors or histamine-2 receptor antagonists [H_2RA]), 58% reported GI symptoms, and high scores on this GI symptom scale correlated with lower quality-of-life assessment scores, regardless of JRA disease activity. This is complicated by the fact that 84% of patients took methotrexate, 55% took anti-TNF-α biologics, and 13% were taking oral corticosteroids. Methotrexate and corticosteroids may especially also cause GI symptoms. Nevertheless, dyspepsia is a common symptom in children with JRA, and concomitant NSAID therapy is a likely contributor.

4.2. Cardiovascular and Renal Effects

It is difficult to prospectively assess the long-term cardiovascular and renal risks of the selective or nonselective NSAIDs in JRA patients whose disease, and need to use these medications, persist well into adulthood.

Chronic NSAID use in adults is known to cause or exacerbate hypertension. Increasing data in the pediatric population point to hypertension becoming an increasingly prevalent chronic condition, particularly in Western society where estimates of around 4% of children have blood pressures above the 99% percentile for their age, sex, and weight.[45] Together with increasing prevalence of young onset type II diabetes and clustering with the metabolic syndrome, this points to important changes in the long term cardiovascular risks in this population.

A review of the published literature suggests that renal-related adverse events are rarely reported during clinical trials. In one recent trial (rofecoxib versus naproxen, 12-week double-blind phase with 52-week open-label phase)[24] in 310 JRA patients, 1 patient receiving naproxen experienced an elevation of creatinine and 2 patients experienced edema during the double-blind phase of the study. During the open-label phase of the study, 3 patients receiving rofecoxib developed edema. In a trial of flurbiprofen, 9% of patients developed hematuria.[34] No other trials report overt renal adverse events. Sporadic reports of renal events in children with JRA receiving NSAIDs exist in the literature. The most common of such events appears to be acute, idiosyncratic renal failure, which generally occurs early in therapy and is reversible on cessation of the offending therapy.[9] This is also known to occur in otherwise healthy children who take brief courses of NSAID treatment for other indications, such as fever associated with infections. Other reported renal complications include renal papillary necrosis, nephrotic syndrome, and interstitial nephritis. The precise incidence of such events cannot be determined, but they seem rare. This is corroborated by a 4-year prospective study of 226 JRA patients taking NSAIDs for a median of 1.3 years of previous use (range 0.5-8 years).[46] Only 0.4% of these patients developed renal abnormalities, which were limited to abnormal urinalyses (4 patients with hematuria, and 16 with isolated proteinuria, sometimes in the same patient). No patient developed hypertension or elevated serum creatinine, and no other renal adverse events were reported.

Similarly, though hypertension may be an unusual complication during pediatric NSAID use, it could evolve as children continue NSAID use into adulthood and begin to develop other cardiovascular risk factors such as such as obesity or complications of smoking. Furthermore, recent evidence suggests an increase in the background prevalence of cardiovascular risk factors such as increased body mass index and increased blood pressure among children and adolescents in general.[47] These risk factors that originate during childhood may continue into adulthood.[48] This epidemiologic factor may further increase the chances of NSAID treatment causing cardiovascular complications as children progress into adulthood.

4.3. Developmental Effects

There have been no specific studies of the possible effects of NSAID therapy on development. However, the following observations about adults with JRA provide some insight into the likely course of development. First, even though adults who have had JRA have a significantly higher rate of disability, depression, and employment problems compared to their counterparts who have not had JRA, a large proportion of these adults who have had JRA do reach a high level of education, are employed, and/or are married or otherwise report a good ability to form interpersonal relationships.[49, 50, 51] A significant proportion of these adults have short stature due to their previous JRA or its treatment. Yet, this proportion is decreasing as better medical therapies for JRA, a better understanding of the role of nutrition in JRA, and the availability of recombinant human growth hormone have evolved.[52, 53] Most JRA patients reach full sexual maturity, albeit often with significant delay.[54] Since a high proportion of JRA patients receive chronic NSAID therapy, these observations taken together suggest little detectable effect on development.

4.4. Hepatic Effects

Hepatic effects were commonly observed during the era when aspirin was the primary anti-inflammatory agent used in JRA. These included elevations of transaminases and other hepatic disorders, including rarely acute liver failure. As other NSAIDs became available, liver toxicity was subject to scrutiny. Elevated transaminases or bilirubin were, however, only rarely reported in NSAID trials, though this may be confounded by the small number of patients in many of the early trials. Larger trials report a 2% transaminase elevation with ibuprofen,[29] 6% with naproxen,[33] 2-6% with rofecoxib,[24] and in one trial, incidence rates of bilirubin elevations ranging from 7-20% with meloxicam vs. 13% with naproxen.[23] In general, hepatic adverse effects appear to be rare in NSAID trials, and generally appear related to viral infections such as Hepatitis A or Epstein-Barr virus.[24] Similarly, severe hepatotoxicity has only rarely been reported in the literature in conjunction with NSAID therapy for JRA, and has usually been confounded by the presence of the macrophage activation syndrome in patients with systemic disease.[10] NSAID therapy, however, was sometimes considered a triggering factor for this syndrome. Long-term hepatic effects are also difficult to assess, and often confounded by other factors such as methotrexate use, well known for hepatic toxicity.

4.5. Cutaneous Effects

Cutaneous effects of NSAIDs vary in type and frequency depending on the NSAID. In clinical trials of NSAIDs in JRA, notable clinical events included vesicular rashes noted in 30% of patients taking oxaprozin.[35] In other studies that reported such data (including naproxen, meloxicam, and rofecoxib), rash was generally seen in 0-10% of the patients.[23, 24] Such rashes were highly variable in their manifestations and presumed etiology. However, although rashes were often labeled as allergic in nature or related to a hypersensitivity reaction, severe cutaneous adverse reactions (SCAR, including erythema multiforme [EM] Stevens-Johnson syndrome [SJS], and toxic epidermal necrolysis [TEN]) were not reported in the randomized trials. These adverse events have, however, been reported for most if not

all NSAIDs in postmarketing safety surveillance, and all NSAIDs are labeled for these potentially fatal SCAR adverse events.

Review of relevant literature reports reveals a variety of rashes that have been attributed to NSAID therapy. The most commonly reported is pseudoporphyria, which has been most commonly associated with naproxen therapy, and has been reported to occur in 12% of JRA patients taking naproxen.[55, 56] However, pseudoporphyria has been reported sporadically with almost every NSAID, including 1 event with rofecoxib in a clinical trial,[24] and 1 literature report of this effect in an adolescent taking celecoxib.[57]

5. PREDICTED AND KNOWN SAFETY PROFILES OF SELECTIVE COX-2 INHIBITORS IN CHILDREN

Previous clinical trial experience with selective COX-2 inhibitors in JRA is limited to a single trial of rofecoxib versus naproxen.[24] This trial was a 12-week, multicenter, randomized, double-blind, double-dummy, active comparator-controlled, non-inferiority study with a 52-week open-label active comparator-controlled extension. A total of 310 children (ages 2–11 yrs) and adolescents (ages 12–17 yrs) were randomized to treatment. Children received rofecoxib [0.3 mg/kg/day up to 12.5 mg/day (LD) or 0.6 mg/kg/day up to 25 mg/day (HD)] or naproxen 15 mg/kg/day as oral suspensions. Adolescents received rofecoxib (LD) 12.5 mg/day (base study only) or (HD) 25 mg/day, or naproxen 15 mg/kg/day (maximum 1000 mg/day) as tablets.

The predominant safety findings were as follows. In the double-blind portion of the study, the 3 most commonly reported adverse events were abdominal pain, upper abdominal pain, and headache. GI adverse events occurred in 26.6%, 32.0%, and 39.6% of patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively. No clinical adverse events of hypertension, congestive heart failure, renal insufficiency, or related terms were identified. However, there were 2 adverse events consistent with edema, one in the HD-rofecoxib group and one in the naproxen group. There were no reported cases of serious upper GI events (ie, perforations, ulcers, bleeds) or thrombotic cardiovascular events in either the base or extension studies. Mild to moderate allergic-type skin and hypersensitivity reactions occurred in 4.6%, 5.0%, and 4.0% patients in the LD-rofecoxib, HD-rofecoxib, and naproxen groups, respectively.

In the open-label portion of the study, there was one drug-related case of pseudoporphyria in the HD-rofecoxib group. Otherwise, the profile of adverse events reported during the open-label phase was similar to the double-blind phase of the study.

In summary, rofecoxib was generally well tolerated. Adverse events and laboratory abnormalities were comparable between rofecoxib and naproxen, and within the parameters of what has commonly been reported in past pediatric NSAID trials.

6. REGULATORY BACKGROUND OF NSAIDS WITH A JRA INDICATION AND THE REGULATORY HISTORY OF THE CELECOXIB JRA STUDY

Few NSAIDs are labeled and indicated by FDA for the relief of the signs and symptoms of JRA. They include tolmetin, naproxen, ibuprofen, oxaprozin, meloxicam, and rofecoxib (rofecoxib has since been removed from the market due to cardiovascular adverse effects in adults). For three of these drugs (oxaprozin, rofecoxib, and meloxicam), the respective sponsors fulfilled a PWR, which resulted in an indication for JRA and pediatric exclusivity. Table 1 provides a summary of controlled clinical studies that provided supportive data for the JRA indications of the various NSAIDs (except in the case of oxaprozin, for which an open-label study served as the basis for pediatric labeling), presented in approximate chronological order of approval date. None of the JRA studies with NSAIDs were placebo-controlled, since it is difficult to conduct placebo-controlled studies in children, particularly for drugs that have been shown to benefit adults. The scope of these clinical studies/programs ranges from 59 total patients in a single study for oxaprozin to 434 total patients in 2 clinical studies for meloxicam, which was approved in August 2005. Similar to the approved NSAIDs, relatively few patients were included in the clinical studies that supported the FDA approval of JRA indications for the DMARDs methotrexate (127 total patients) and sulfasalazine (69 total patients) and the BRM etanercept (69 total patients).[58, 59, 60] The size and scope of these studies furthermore underscores the challenges in studying this patient population.

Table 1 NSAIDs (Non-Salicylates) with a US Indication for Juvenile Rheumatoid Arthritis

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Drug / Reference	Treatments and Number of Patients	Study Design	Primary Endpoint for Controlled Studies
Tolmetin			
Tolmetin Levinson et al. 1977[31]	Tolmetin 15-30 mg/kg/d; N=53 Aspirin 50-100 mg/kg/d; N=54	12-week double-blind, parallel group, multicenter, superiority	Percent improvement in index of active joints
Naproxen			
Naproxen Makela, 1977[61]	Naproxen 6.5 mg/kg/d Aspirin 60 mg/kg/d 18 total patients	12-week, randomized, double-blind, crossover	Physician preference for drug
Naproxen Moran et al., 1979[32]	Naproxen 10 mg/kg/d Aspirin 80 mg/kg/d 23 total patients 33 patients in open-label	8-week randomized, double-blind, crossover (2 4-week periods) 12-month open-label	Functional grading, joint involvement, grip strength, physician's opinion of treatment, laboratory tests
Naproxen Kvien et al., 1984[62]*	Naproxen 10 mg/kg/d ASA 75 mg/kg/d 80 total patients	24-week randomized, parallel group, double-blind	Percent improvement in index of active joints
Ibuprofen			
Ibuprofen Giannini et al., 1990[29]	Ibuprofen 30-40 mg/kg/d; N=45 Aspirin 60-80 mg/kg/d; N=47	12-week, randomized, double-blind, parallel-group, multicenter, superiority	Physician's Global Assessment (Study powered to detect a 30% difference between treatment groups in physician's global assessment)
Ibuprofen Giannini et al., 1990[29]	Ibuprofen 30 mg/kg/d; N=11 Ibuprofen 40 mg/kg/d; N=27 Ibuprofen 50 mg/kg/d; N=46	24-week, open-label, multidose, multicenter	
Oxaprozin			
Oxaprozin Bass et al., 1985[35]*	Oxaprozin 10-20 mg/kg/d, N=59	12-week open-label with 9 month extension	Physician's Global Assessment

*Data from study presented in US package insert for drug.

Table 1 NSAIDs (Non-Salicylates) with a US Indication for Juvenile Rheumatoid Arthritis

Drug / Reference	Treatments and Number of Patients	Study Design	Primary Efficacy for Controlled Studies
Rofecoxib			
Rofecoxib Reiff et al. 2006[24]*	Double-blind: Rofecoxib 0.3 mg/kg/d up to 12.5 mg/d; N=109 Rofecoxib 0.6 mg/kg/d up to 25 mg/d; N=100 Naproxen 15 mg/kg/d; N=101 Open-label: Rofecoxib 0.6 mg/kg/d up to 25 mg/d; N=160 Naproxen 15 mg/kg/d; N=67	12-week, randomized, double-blind, double-dummy, active comparator-controlled, multicenter, non-inferiority 52-week open-label active comparator-controlled extension	Time-weighted average proportion of patients meeting ACR Pediatric 30 Response criterion (Non-inferiority margin = 0.5 for the ratio of the percentage patients achieving an ACR Pediatric 30 Response [rofecoxib vs. naproxen])
Meloxicam			
Meloxicam Ruperto et al. 2005[23]*	Meloxicam 0.125 mg/kg/d; N=73 Meloxicam 0.25 mg/kg/d; N=74 Naproxen 10 mg/kg/d; N=78	12-week randomized, double-blind, double-dummy, multicenter, superiority with a 40-week double-blind extension	ACR Pediatric 30 Response at Month 3 (90% power to detect a 20% treatment difference)
Meloxicam Gedalia et al. 2004[28]* (abstract)	Double-blind: Meloxicam 0.125-0.25 mg/kg/d; N=62 Meloxicam 0.25-0.375 mg/kg/d; N=72 Naproxen 10-15 mg/kg/d; N=75 Open-label: Meloxicam 0.375 mg/kg/d; N=191	12-week randomized, double-blind, active-controlled 12-week open-label extension	ACR Pediatric 30 Response

*Data from study presented in US package insert for drug.

Regarding celecoxib, discussions were initiated with the FDA for the design of a pediatric program in 1999 that would, when completed, provide information to better inform appropriate labeling for the use of celecoxib in JRA. Agreement was reached on a final PWR, issued in January 2002. The study design and labeling considerations were based on agreements reached between the Sponsor and the Agency and were consistent with the pediatric legislation in effect (BPCA, 2002). The PWR was comprised of a single study (Study N49-01-02-195, hereafter referred to as Study 195) assessing efficacy and safety of celecoxib in the JRA population and including pharmacokinetic (PK) assessments. In September 2002, the Sponsor submitted the final protocol, incorporating the design elements described in the PWR. In December 2003, legislation (PREA) was enacted that described expectations for clinical trials in children. This legislation replaced the FDA Pediatric Rule and applied to all product submissions from April 1999. The work underway through the PWR was considered by the Sponsor to meet PREA obligations as well as the agreed requirements for consideration of exclusivity under BPCA.

The scope of celecoxib Study 195 was similar to studies with other NSAIDs that successfully fulfilled a PWR. The first patient was enrolled in Study 195 in October 2002 and the last patient completed the study in April 2005. Therefore, a majority of the conduct of Study 195 occurred before 1) Merck's worldwide withdrawal of Vioxx® (rofecoxib) in September 2004; 2) the suspension of 2 chemoprevention studies involving long-term treatment with celecoxib in December 2004; and 3) the adoption of harmonized labeling language, including a boxed warning, for cardiovascular safety issues regarding all NSAIDs as a class in 2005. When the new cardiovascular safety information emerged from the rofecoxib and celecoxib chemoprevention studies in September and December 2004, respectively, the Sponsor promptly notified investigators of all ongoing celecoxib clinical studies of the relevant cardiovascular safety information. In December 2004, FDA requested information related to the status of ongoing JRA Study 195, as well as implementation of a Data Safety Monitoring Board (DSMB) to assure patient safety. Investigators were provided with a revised informed consent document, which was updated with cardiovascular safety information pertaining to the celecoxib chemoprevention trials, and were instructed to inform ongoing patients of this new safety information and obtain updated informed consent forms from the patients in Study 195. The DSMB concluded that there were no safety concerns that should warrant discontinuation of the study. The study was continued until completion, which occurred in April 2005.

In January 2006, a meeting was conducted between the Sponsor and the Agency to agree on the format and content of a submission of the results from Study 195 and other supporting documentation. As stipulated in the PWR, an sNDA was submitted in June 2006 to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the purposes of completing the Sponsor's obligation to fulfill the requirements of the PWR for celecoxib. In August 2006, FDA officially filed the efficacy supplement submitted for review as sNDA 20-998/S-021, and assigned priority review status to the pediatric supplement, as required under the regulations. In addition, the Agency notified the Sponsor that the requirements specified in the PWR had been met, therefore qualifying the Sponsor to receive pediatric exclusivity for CELEBREX. The review of sNDA 20-998/S-021 is currently ongoing at FDA.

In summary, the size and scope of Study 195 was similar to clinical trials conducted with other NSAIDs in JRA. The Sponsor's efforts to study celecoxib in JRA patients were undertaken to provide sufficient information to permit the appropriate labeling for use of celecoxib in the pediatric population, consistent with the intent of the pediatric regulations.

7. EFFICACY AND SAFETY PROFILE OF CELECOXIB IN JRA PATIENTS

The data summarized above have demonstrated that the group of conditions characterized by the term JRA is a significant health issue affecting many thousands of children in the US. Despite advances in disease modification over recent years, and better understanding of some of the pathophysiological aspects of JRA, NSAIDs continue to play a major role in treatment. Hence, in consultation and agreement with FDA, the Sponsor undertook a PK, efficacy, and safety study of celecoxib in JRA patients (Study 195), which was designed to fulfill the requirements of the PWR and incorporate all of the requirements described therein. This section summarizes efficacy and safety results of Study 195.

7.1. Investigational Plan for Study 195

7.1.1. Study Design

Study 195 was a 12-week, randomized, double-blind, active-controlled, parallel-group, multicenter, non-inferiority study comparing the efficacy and safety of celecoxib with the efficacy and safety of naproxen for treatment of the signs and symptoms of pauciarticular, polyarticular, and systemic-onset (with currently inactive features) JRA. The study also included an optional 12-week, open-label extension phase after the initial double-blind phase.

Patients who met the inclusion and exclusion criteria for the study (described below) were randomly assigned to 1 of the 3 treatment groups (investigational suspension of celecoxib at a target dosage of 3 or 6 mg/kg BID or naproxen suspension at a target dosage of 7.5 mg/kg BID) in a 1:1:1 ratio. Clinic visits during the double-blind portion of the study occurred at Screening, Baseline, and at Weeks 2, 4, 8, and 12 (or early termination). Patients who entered the open-label portion of the study received celecoxib at a target dose of 6 mg/kg BID. Visits during the open-label portion of the study occurred at Weeks 16 and 24.

7.1.2. Patient Population

Patients who were between 2 and 16 years of age (inclusive) at the baseline visit and weighed ≥9 kg were eligible for the study. Patients were to have a diagnosis of polyarticular or pauciarticular course of JRA as determined by the ACR criteria and were required to have ≥1 swollen joint and ≥1 joint with limitation of motion (could be the same joints). Patients with systemic-onset JRA who had polyarticular or pauciarticular course were eligible. It was required that the patients be candidates for NSAID therapy in the investigator's opinion. At the screening visit, the Physician's Global Assessment of Disease Activity and Parent's Global Assessment of Overall Well-Being were required to be ≥10 mm on a 100-mm visual analog scale (VAS).

Exclusion criteria included the presence of active systemic manifestations of JRA; the patient's starting or changing the dose regimen of methotrexate within 8 weeks prior to

receiving the first dose of study medication (permitted at doses ≤1 mg/kg/week or 40 mg maximum permitted weekly dosage); and the patient's starting or changing the dose regimen of DMARDs (other than methotrexate), BRMs, or IV immunoglobulins or other immunosuppressants within 12 weeks or injectable gold salts within 16 weeks prior to receiving the first dose of study medication. Initiation of therapy with oral corticosteroids or changes in the dose regimen within 4 weeks of Screening was prohibited (doses up to 0.2 mg/kg/day or 10 mg prednisone or equivalent per day, whichever was less, were allowed). Injections of corticosteroids (intravenous, intramuscular, intra-articular, or soft tissue) within 4 weeks of Screening were not allowed. Patients were not to have dose adjustments of concomitant medications such as oral corticosteroids, DMARDs, and BRMs during study participation. Patients could receive a single joint injection after the double-blind portion of the study, if necessary.

7.1.3. Study Medication

Naproxen was chosen as the active comparator in Study 195 because it is the standard NSAID of choice in the pediatric rheumatology community and is approved by FDA for the treatment of JRA. The dosing used for naproxen (approximately 7.5 mg/kg BID) was based upon recommendations from the pediatric rheumatology community for a therapeutic range of 10 to 20 mg/kg/day[63] and is consistent with the labeled dose of naproxen for treatment of JRA. The dosing of celecoxib (approximately 3 and 6 mg/kg BID) in JRA patients was extrapolated from the recommended adult dose of celecoxib for RA. The actual doses (in mg) administered to these patients followed an allometric pattern.[64] For example, clearance (unadjusted for body weight) in a 10-kg patient was assumed to be approximately 25% of that in a 70-kg adult. Hence, a 10-kg patient received either 25 or 50 mg BID in Study 195 for the low and high dose groups, which are 25% of the approved adult RA doses of 100 and 200 mg BID, respectively. However, a preliminary investigation of the PK of celecoxib in older children and adolescents with cancer suggested they had increased clearance (unadjusted for body weight) of the drug relative to adults.[65] Therefore, 300 mg BID (600 mg total daily dose) was administered to JRA patients weighing >50 kg. Although this dosing exceeds the usual adult RA dose of 400 mg per day, it was adopted to avoid using a dosage that was too low to be efficacious in heavier children. At the time the study was designed, data from extensive safety studies in adults using celecoxib in doses up to 800 mg per day (administered as 400 mg BID) showed no increased risk of adverse events at these higher doses compared to nonselective NSAIDs, including in many patients with significant comorbidities.[1]

The study medication dosing targets described above were implemented by administration of fixed dosages determined according to weight category (defined by patient weight at Baseline) as shown in Table 2, producing a range of actual delivered dosages in mg/kg for each target dosage and weight category. The volume of study medication administered during the open-label portion of the study was determined by the patient's weight at the Week 12 visit. The volume assigned at the Baseline and Week 12 visits was maintained throughout the respective phases of the study, even if the patient's weight subsequently changed during that phase. The suspension was administered BID before breakfast and before bedtime.

Table 2. Study Medication Dosage for JRA Patients by Weight Category, Study 195

Patient Weight	Dosage Administered / Delivered Dosage Range (Highest to Lowest Weight)		
	Celecoxib 3 mg/kg BID Target	Celecoxib 6 mg/kg BID Target	Naproxen 7.5 mg/kg BID Target
9-12 kg	25 mg BID	50 mg BID	62.5 mg BID
	2.1-2.8 mg/kg BID	4.2-5.6 mg/kg BID	5.2-6.9 mg/kg BID
13-25 kg	50 mg BID	100 mg BID	125 mg BID
	2.0-3.8 mg/kg BID	4.0-7.7 mg/kg BID	5.0-9.6 mg/kg BID
26-37 kg	75 mg BID	150 mg BID	187.5 mg BID
	2.0-2.9 mg/kg BID	4.1-5.8 mg/kg BID	5.1-7.2 mg/kg BID
38-50 kg	100 mg BID	200 mg BID	250 mg BID
	2.0-2.6 mg/kg BID	4.0-5.3 mg/kg BID	5.0-6.6 mg/kg BID
>50-100 kg[a]	150 mg BID	300 mg BID	500 mg BID
	1.5-2.9 mg/kg BID	3.0-5.9 mg/kg BID	5.0-9.8 mg/kg BID

BID = Twice daily

[a] Upper limit of 100 kg shown only to illustrate potential lowest delivered dosage; no upper weight limit for patients was specified in the study protocol.

7.1.4. Efficacy Assessments

The efficacy assessments that were chosen for Study 195 are consistent with recommendations from relevant literature and draft and current FDA guidelines.[66,67,68,69, 70] The JRA 30% Definition of Improvement (JRA-30 DOI), now known formally as the ACR Pediatric 30 Response, is recommended as a validated efficacy endpoint in the 1999 FDA guidance for products for the treatment of RA (JRA section) and therefore was included as the primary efficacy measure. The ACR Pediatric 30 Response is derived from the following 6 core set variables: Physician's Global Assessment of Disease Activity (100-mm VAS); Parent's Global Assessment of Overall Well-Being (Childhood Health Assessment Questionnaire [CHAQ] subsection; 100 mm VAS); Parent's Assessment of Physical Function (CHAQ Disability Index; Grades 0-3); number of joints with active arthritis (73 total joints assessed); number of joints with limited range of motion (67 total joints assessed); and laboratory marker of inflammation (C-reactive protein [CRP]). Efficacy according to the ACR Pediatric 30 Response criterion is defined as ≥30% improvement in ≥3 core set variables and at most 1 core set variable worsening by >30%.

A non-inferiority margin of 25% was prospectively specified in discussions with FDA to rule out a clinically relevant difference between each celecoxib treatment group and the naproxen group. It should also be noted that the non-inferiority margin of 25% is further supported by a meta-analysis derived from previous placebo-controlled studies in children with JRA.[71] From this meta-analysis, the range for the percentage of placebo responders was 8.8% to 35.9%. Therefore, assuming that the true incidence of responders is ≥60% for naproxen, confidence intervals which demonstrate non-inferiority between celecoxib and naproxen using a margin of 25% would also provide evidence indirectly that the celecoxib response is at least greater than placebo.

Non-inferiority hypothesis testing was 1-sided at the 2.5% level of significance, or equivalently, non-inferiority of a celecoxib dose was claimed if the lower limit of the 95% 2-sided confidence interval (CI) for the difference in the proportion of ACR Pediatric 30 responders (π_C-π_N, where π_C is the percentage of responders in the celecoxib treatment group and π_N is the percentage of responders in the naproxen treatment group) was above –25%. These analysis criteria were determined in consultation with the Agency.

A number of secondary efficacy assessments, including the individual components (core set) of the ACR Pediatric 30 Response and Parent's Assessment of Child's Arthritis Pain (CHAQ Subsection), were also analyzed as change from Baseline at Weeks 2, 4, 8, and 12 (final visit). The Pediatric Quality of Life Inventory (PedsQL™) was conducted at Baseline and Week 12 (final visit). Post-hoc exploratory analyses were performed for the percentage of patients with either pauciarticular course JRA or polyarticular course JRA who met the ACR Pediatric 30 Response criterion. In addition, post-hoc exploratory analyses were performed for the ACR Pediatric 30 Response rates of patients who were using DMARDs or BRMs at baseline and during the course of the study and those who did not use DMARDs or BRMs during the course of the study.

Efficacy data for the open-label phase of the study were summarized with baseline defined as the last observation prior to the first dose of open-label study medication for the patients enrolled in the open-label phase of the study.

7.1.5. Safety Assessments

Safety was assessed with reporting of adverse events, clinical laboratory tests, and vital-sign measurements at Baseline and at each post-baseline visit. (Not all assessments were performed at all visits.) Information related to vital signs at each visit was collected as a single measurement after the patient had been in a sitting position for at least 5 minutes. Physical examination and a developmental history were obtained by the investigators at Screening and at Weeks 8, 12, and 24 to capture any deleterious treatment effects on growth and development. Any adverse change in development or loss of developmental milestones occurring during the course of the study was to be captured as an adverse event. A slit-lamp eye examination to assess for uveitis was performed at Screening and at Weeks 12 and 24.

All adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated by treatment group and system organ class. Adverse events obtained within 28 days after the last dose of study medication were included for all incidence tables. Clinical laboratory parameters and vital signs that were collected up to 5 days following the last dose of study medication were included for these analyses.

7.2. Patient Disposition and Baseline Characteristics of Study 195

All 242 patients enrolled and randomized in Study 195 received at least 1 dose of study medication, and the majority completed the double-blind phase (87%-89% by treatment group) (Table 3). The most common reason for early withdrawal from the double-blind

phase in the celecoxib 6 mg/kg BID treatment group was for adverse events (8.5%, versus 3.6%-3.9% in the other groups).

Table 3. Patient Disposition in Double-Blind Phase, Study 195*

Disposition / Reason for Withdrawal[a]	Celecoxib 3 mg/kg BID (N = 77)	Celecoxib 6 mg/kg BID (N = 82)	Naproxen 7.5 mg/kg BID (N = 83)
Completed double-blind phase, n (%)	67 (87.0)	71 (86.6)	74 (89.2)
Withdrawn from double-blind phase, n (%)	10 (13.0)	11 (13.4)	9 (10.8)
Adverse event	3 (3.9)	7 (8.5)	3 (3.6)
Protocol violation	0 (0.0)	1 (1.2)	1 (1.2)
Consent withdrawn	4 (5.2)	2 (2.4)	1 (1.2)
Lost to follow-up	1 (1.3)	0 (0.0)	0 (0.0)
Lack of efficacy	2 (2.6)	1 (1.2)	4 (4.8)

*All Randomized Patients
Abbreviations: BID = Twice Daily
[a] Reasons are mutually exclusive and exhaustive categories.

Of the 212 patients who completed the double-blind phase, 202 entered the open-label phase (62 from the celecoxib 3 mg/kg BID treatment group, 70 from the celecoxib 6 mg/kg BID treatment group, and 70 from the naproxen 7.5 mg/kg BID treatment group). The most common reason why patients did not enter the open-label phase of the study was withdrawal of consent (7 of 10 patients). All 202 patients enrolled in the open-label phase of the study received at least 1 dose of open-label study medication, and the majority (96.5%) completed the open-label phase of the study. The reasons for early withdrawal from the open-label phase of the study were adverse events (1.5%), consent withdrawn (1.0%), protocol violation (0.5%), and protocol-specified withdrawal criteria (0.5%).

The treatment groups in the double-blind phase were well matched with respect to demographics, baseline clinical characteristics such as duration of illness, course of arthritis, and systemic onset, and antirheumatic medications used at Baseline (Table 4). The majority of patients enrolled were white (53% to 63% by treatment group reported as white, with race not listed for nearly one-third of patients) and a majority were female (65% to 77% by treatment group). From 70% to 75% of patients by treatment group were between the ages of 8 and 16 years. Thirty-nine patients (16.1%) were under the age of 5 at the time of enrollment, and 22 patients (9.1%) had systemic onset of JRA. Overall, the study population appeared to be representative of the general JRA population.[3] Approximately half of the patients in each treatment group were receiving standard-of-care treatment (DMARDs and/or BRMs) at the time of enrollment. Of those patients receiving standard-of-care therapy, the majority were receiving methotrexate (which, per protocol, was to be administered only at stable dosages ≤1 mg/kg/day and ≤40 mg/week). The majority of patients (74% to 83% by treatment group) were not receiving oral corticosteroid therapy at the time of enrollment.

Table 4. Patient Baseline Characteristics, Study 195*

Baseline Characteristic	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)	10.44 (4.09)	10.16 (4.24)	10.39 (3.92)
Distribution by age category, n (%)			
2-4 years	13 (16.9)	16 (19.5)	10 (12.0)
5-7 years	9 (11.7)	9 (11.0)	11 (13.3)
8-12 years	31 (40.3)	35 (42.7)	35 (42.2)
13-16 years	24 (31.2)	22 (26.8)	27 (32.5)
Gender, n (%)			
Female	59 (76.6)	53 (64.6)	59 (71.1)
Male	18 (23.4)	29 (35.4)	24 (28.9)
Race, n (%)			
White	41 (53.2)	47 (57.3)	52 (62.7)
Black	9 (11.7)	7 (8.5)	4 (4.8)
Asian	1 (1.3)	3 (3.7)	1 (1.2)
Not Listed	26 (33.8)	25 (30.5)	26 (31.3)
Duration of JRA in years: mean (SD)	2.71 (2.80)	3.77 (3.42)	3.41 (3.23)
Onset with systemic features: n (%)	4 (5.2)	10 (12.2)	8 (9.6)
Course: n (%)[a]			
Pauciarticular	37 (48.1)	45 (54.9)	46 (55.4)
Polyarticular	40 (51.9)	37 (45.1)	37 (44.6)
Baseline antirheumatic medications, n (%)			
Any DMARD or BRM	39 (50.6)	40 (48.8)	43 (51.8)
Methotrexate[b]	30 (39.0)	29 (35.4)	28 (33.7)
Azathioprine[b]	0 (0.0)	1 (1.2)	0 (0.0)
Hydroxychloroquine sulfate[b]	3 (3.9)	2 (2.4)	5 (6.0)
Sulfasalazine[b]	1 (1.3)	3 (3.7)	3 (3.6)
Etanercept[b]	0 (0.0)	1 (1.2)	0 (0.0)
Combinations	5 (6.5)	4 (4.9)	7 (8.4)
Oral corticosteroids	13 (16.9)	16 (19.5)	22 (26.5)

*All Randomized Patients
Abbreviations: BID = Twice Daily; BRM=biological response modifier; DMARD=disease-modifying antirheumatic drug; JRA = Juvenile Rheumatoid Arthritis; SD = Standard Deviation.
[a] Course was defined by the number of active joints the patient was exhibiting at the Baseline visit.
[b] As the only DMARD or BRM used at Baseline

7.3. Efficacy Results of Study 195

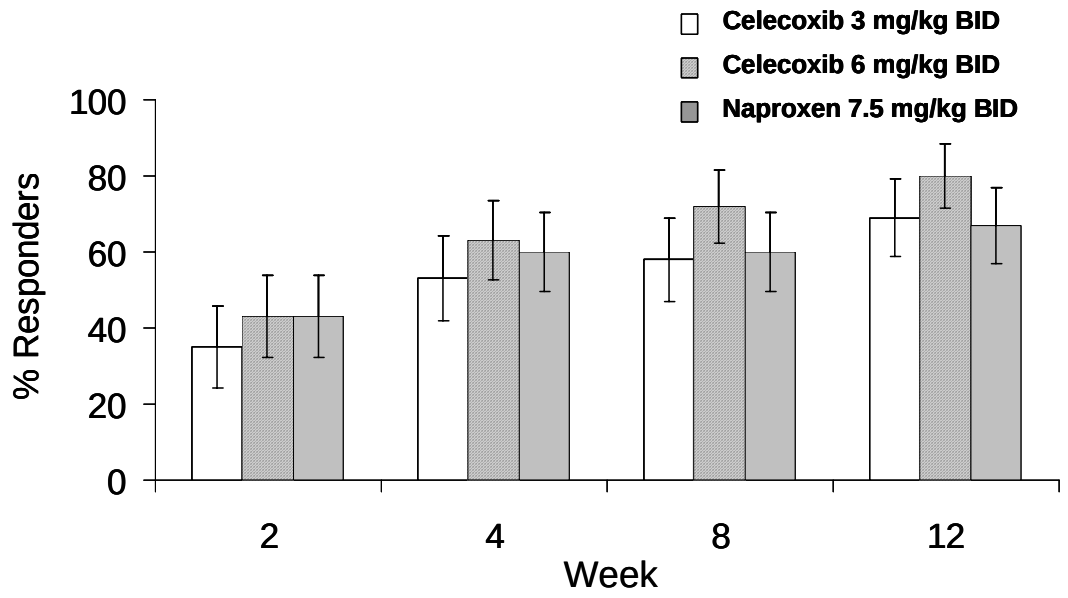
The primary efficacy measure in Study 195 was the percentage of patients who met the ACR Pediatric 30 Response criterion[66] at Week 12, and it is presented in Table 5. The percentage of patients who met the ACR Pediatric 30 Response criterion at Week 12 was 68.8% in the celecoxib 3 mg/kg BID treatment group, 80.5% in the celecoxib 6 mg/kg BID treatment group and 67.5% in the naproxen 7.5 mg/kg BID group. Both celecoxib 3 mg/kg BID and celecoxib 6 mg/kg BID were non-inferior to naproxen 7.5 mg/kg BID in the treatment of the signs and symptoms of JRA at the primary endpoint (Week 12), as well as at all other time points during the double-blind phase of the study (Weeks 2, 4, and 8). Trends in treatment differences favored celecoxib 6 mg/kg BID over naproxen 7.5 mg/kg BID at Weeks 4, 8, and 12, and over celecoxib 3 mg/kg BID at Weeks 2, 4, 8, and 12 (Figure 1).

Table 5. Primary Efficacy Endpoint: ACR Pediatric 30 Response Criterion at Week 12, Study 195*

Statistic	Celecoxib 3 mg/kg BID N = 77	Celecoxib 6 mg/kg BID N = 82	Naproxen 7.5 mg/kg BID N = 83
Number (%) of responders[a]	53 (68.8)	66 (80.5)	56 (67.5)
Comparisons to naproxen[b]			
Difference [95% CI][c]	+ 1.4% [-13.1%, 15.8%]	+ 13.0% [-0.22%, 26.3%]	--
P-value	0.8535	0.0568	--

*Intent-to-Treat Cohort
Note: celecoxib 3 mg/kg BID = 50 mg/5 mL; celecoxib 6 mg/kg BID = 100 mg/5 mL; naproxen 7.5 mg/kg BID = 125 mg/5 mL.
Abbreviations: ACR = American College of Rheumatology; BID = Twice Daily; CI = Confidence Interval
[a] Patients showing ≥30% improvement in ≥3 of 6 ACR Pediatric 30 core set variables and >30% worsening in at most 1 ACR Pediatric 30 core set variable at Week 12
[b] Treatment comparisons using chi-square test and large sample normal approximation CI
[c] Celecoxib minus naproxen

Figure 1 ACR Pediatric 30 Response Rates (95% CIs) at Weeks 2 to 12, Study 195*



* ITT Population
NOTE: p>0.05 for all between-treatment statistical tests at all assessment times.

A post-hoc exploratory analysis of ACR Pediatric 30 Response rates for the subgroups of patients with pauciarticular and polyarticular JRA was performed. The percentage of patients with pauciarticular course JRA who met the ACR Pediatric 30 criterion at Week 12 was 76% (28/37) for the celecoxib 3 mg/kg BID treatment group, 78% (35/45) for the

celecoxib 6 mg/kg BID treatment group, and 76% (35/46) for the naproxen 7.5 mg/kg BID treatment group; corresponding response rates for the polyarticular subgroup were 63% (25/40), 84% (31/37), and 57% (21/37), respectively.

In addition, a post-hoc exploratory analysis of ACR Pediatric 30 Response rates for the subgroups of patients using DMARDs or BRMs at baseline was performed. For patients who were taking DMARDs or BRMs, dose adjustments were prohibited during study participation. The percentage of patients who used DMARDs or BRMs during the study and met the ACR Pediatric 30 criterion at Week 12 was 77 % for the celecoxib 3 mg/kg BID treatment group, 80% for the celecoxib 6 mg/kg BID treatment group, and 60% for the naproxen 7.5 mg/kg/BID treatment group. In the subgroup of patients who did not use DMARDs or BRMs during the study, the ACR Pediatric 30 Response rates were 61% for the celecoxib 3 mg/kg BID treatment group, 81% for the celecoxib 6 mg/kg BID treatment group, and 75% for the naproxen 7.5 mg/kg/BID treatment group.

Secondary measures of efficacy supported the primary endpoint results. Improvements in each of the 6 JRA core set measures from Baseline to Week 12 were comparable or greater in the celecoxib 6 mg/kg BID treatment group compared with the celecoxib 3 mg/kg BID and naproxen 7.5 mg/kg BID treatment groups (Table 6). In each of the 6 JRA core set measures, no statistically significant differences were found between either of the celecoxib treatment groups and naproxen at any time point (apart from the Week-2 comparison of celecoxib 3 mg/kg BID to naproxen 7.5 mg/kg BID for the Physician's Global Assessment of Disease Activity, which showed a significant difference favoring naproxen). The only statistically significant differences in Week-12 results observed between celecoxib dose groups were differences favoring celecoxib 6 mg/kg BID for number of joints with active arthritis ($p=0.0199$) and number of joints with limited range of motion ($p=0.0181$).

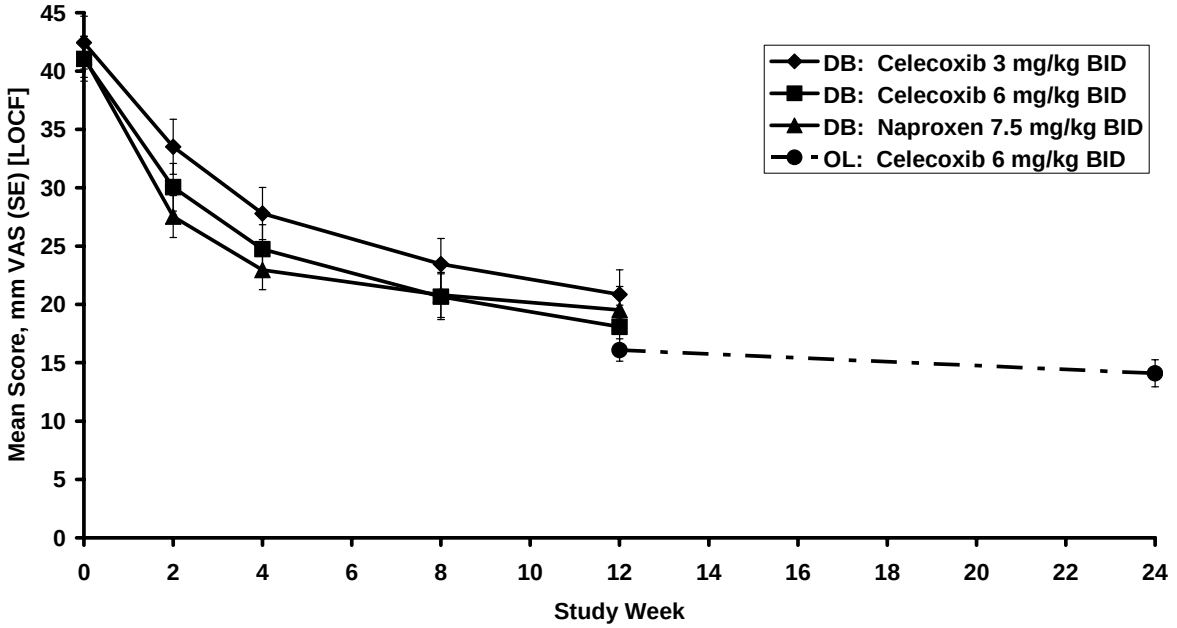
Table 6. Results at Week 12 for ACR Pediatric 30 Response Core Set Measures, Study 195*

Efficacy Measure / Statistic	Celecoxib 3 mg/kg BID N = 77	Celecoxib 6 mg/kg BID N = 82	Naproxen 7.5 mg/kg BID N = 83
Physician's Global Assessment of Disease Activity (100-mm VAS)[a]			
Baseline mean (SE)	42.44 (2.27)	41.05 (1.92)	41.22 (1.76)
LS mean change from Baseline (SE) [b]	-21.07 (1.86)	-23.27 (1.80)	-21.88 (1.79)
P value versus naproxen [b]	0.7526	0.5847	--
Parent's Global Assessment of Overall Well-Being (100-mm VAS)[a]			
Baseline mean (SE)	38.40 (2.46)	42.65 (2.20)	44.95 (2.49)
LS mean change from Baseline (SE) [b]	-17.96 (2.42)	-20.45 (2.34)	-18.25 (2.33)
P value versus naproxen [b]	0.9313	0.5057	
Parent's Assessment of Physical Function (0-3 Numeric Scale)[a]			
Baseline mean (SE)	0.89 (0.06)	0.85 (0.07)	0.87 (0.07)
LS mean change from Baseline (SE) [b]	-0.28 (0.05)	-0.32 (0.05)	-0.31 (0.05)
P value versus naproxen [b]	0.7337	0.8221	--
Number of Joints With Active Arthritis (73 Total Joints Assessed)			
Baseline mean (SE)	8.12 (1.06)	6.68 (0.95)	6.08 (0.66)
LS mean change from Baseline (SE) [b]	-1.94 (0.49)	-3.54 (0.47)	-2.93 (0.47)
P value versus naproxen [b]	0.1456	0.3669	--
Number of Joints With Limited Range of Motion (67 Total Joints Assessed)			
Baseline mean (SE)	6.60 (1.00)	6.26 (0.91)	4.70 (0.58)
LS mean change from Baseline (SE) [b]	-1.14 (0.43)	-2.58 (0.42)	-1.56 (0.42)
P value versus naproxen [b]	0.4898	0.0878	--
Laboratory Marker of Inflammation (C-Reactive Protein, mg/L)			
Baseline mean (SE)	12.25 (3.44)	14.86 (3.47)	16.94 (4.06)
LS mean change from Baseline (SE) [b]	-3.64 (2.87)	-2.67 (2.72)	-0.01 (2.74)
P value versus naproxen [b]	0.3614	0.4922	--

* ITT Population
ACR = American College of Rheumatology; BID = Twice daily; ITT = Intent-to-treat; LS = Least squares; VAS = Visual analog scale
[a] Higher scores indicate poorer well-being or function; negative mean changes indicate improvement.
[b] From ANCOVA model with treatment group as a factor and Baseline value as covariate.

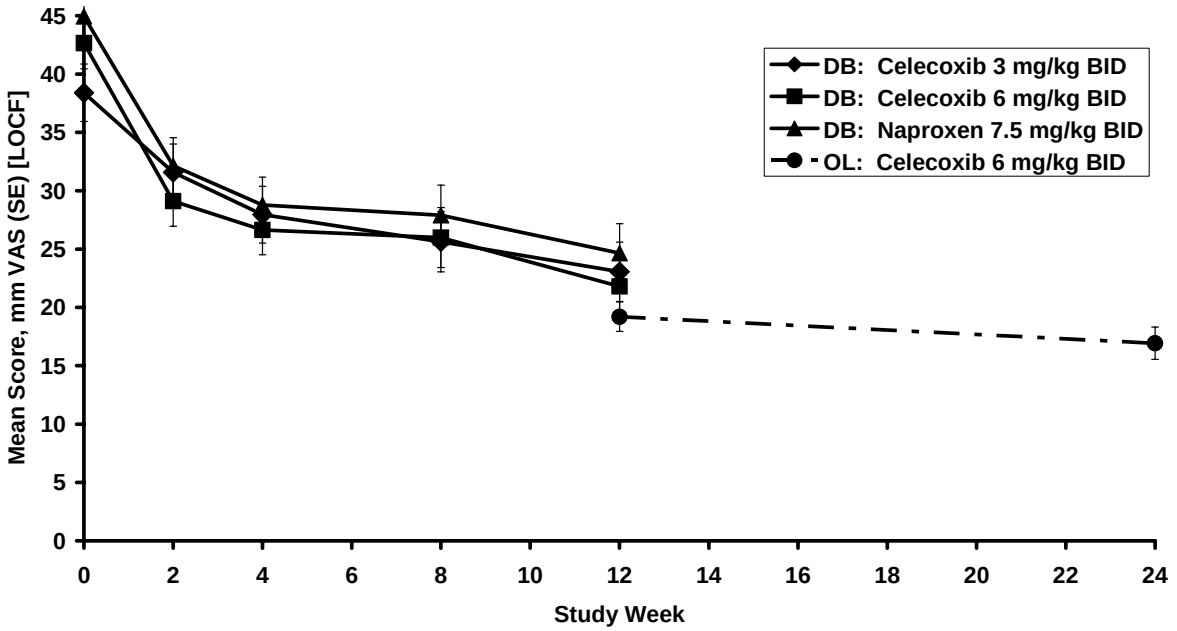
There were also improvements in the Parent's Assessment of Child's Arthritis Pain (CHAQ subsection) in each treatment group and there were no statistically significant differences among any of the treatment groups. For each of the above measures, improvements were apparent as early as Week 2 in celecoxib-treated patients, and the response to celecoxib treatment was durable in the 12-week, open-label extension phase of the study, as evidenced by sustained efficacy results after 24 weeks of treatment that were similar to those observed after 12 weeks of treatment, as shown in Figure 2 through Figure 8.

Figure 2 Physician's Global Assessment of Disease Activity (100-mm VAS) in Double-Blind and Open-Label Phases, Study 195*



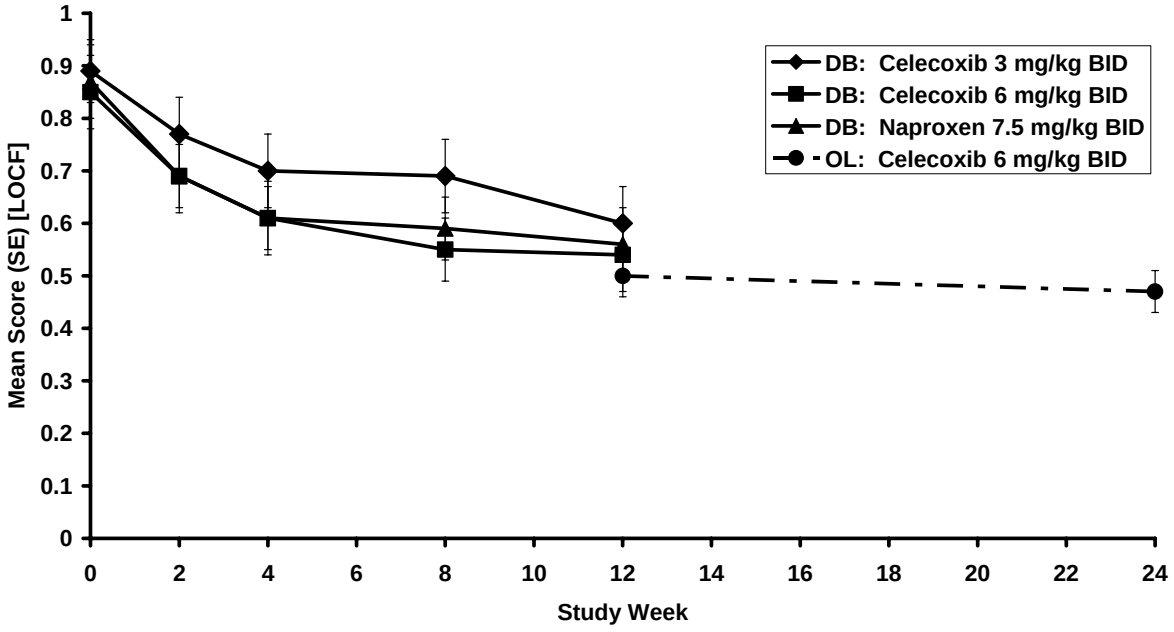
* ITT Population
BID = Twice daily; DB = Double-blind phase; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label phase; VAS = Visual analog scale
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 3 Parent's Global Assessment of Child's Overall Well-Being (100-mm VAS) in Double-Blind and Open-Label Phases, Study 195*



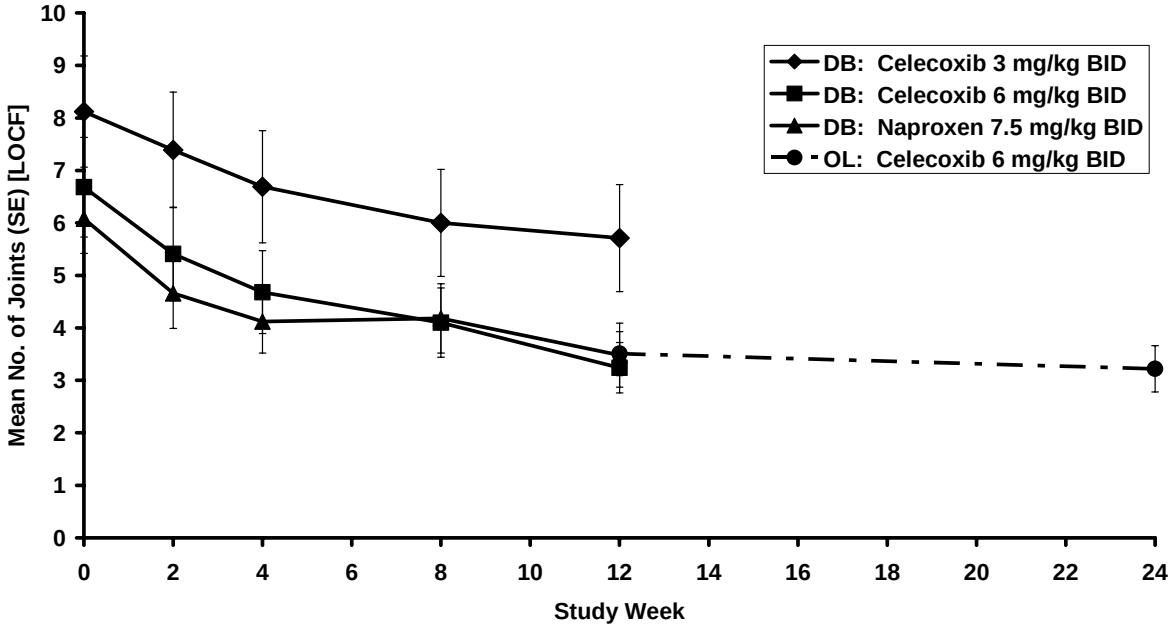
* ITT Population
BID = Twice daily; DB = Double-blind phase; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label phase; VAS = Visual analog scale
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 4 Parent's Assessment of Physical Function (0-3 Numeric Scale) in Double-Blind and Open-Label Phases, Study 195*



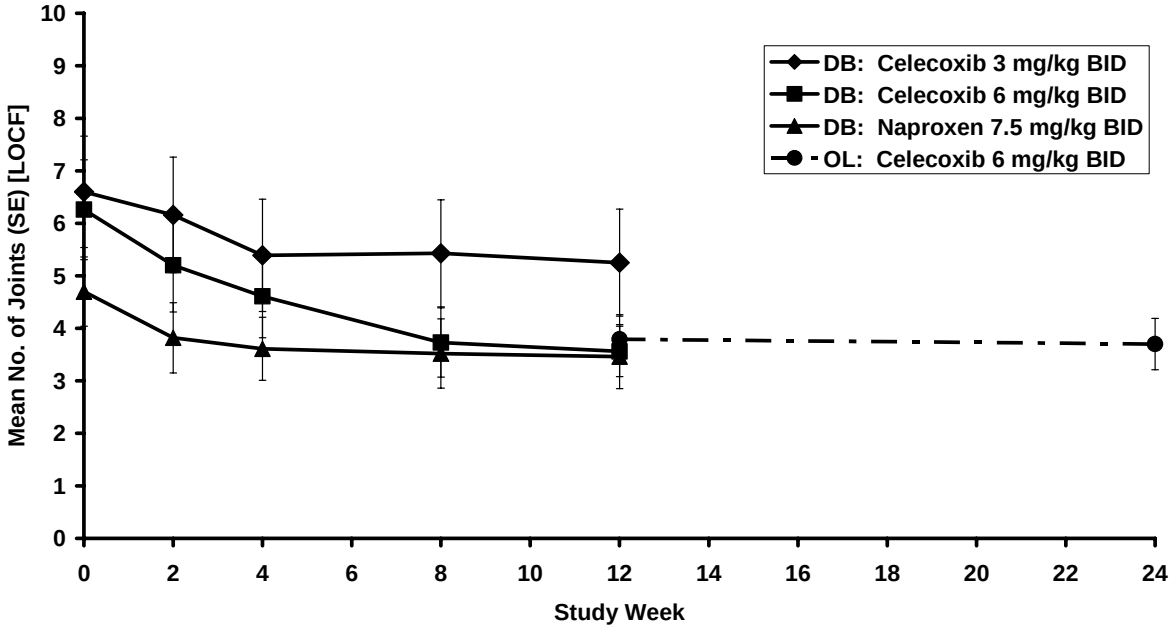
* ITT Population
BID = Twice daily; DB = Double-blind; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 5 Number of Joints with Active Arthritis in Double-Blind and Open-Label Phases, Study 195*



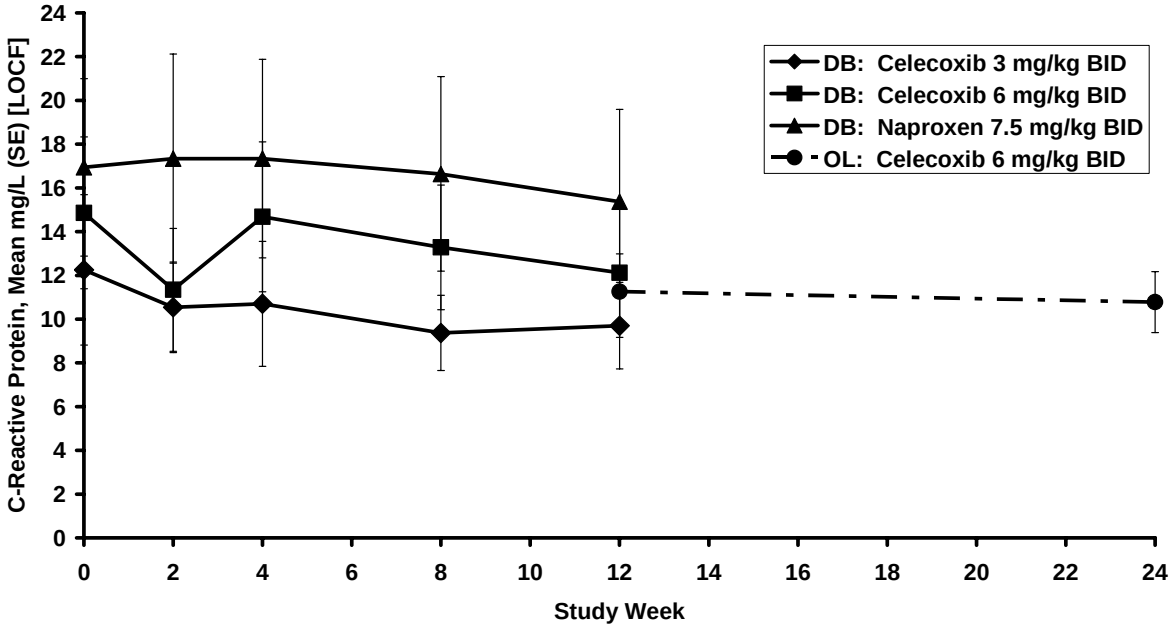
* ITT Population
BID = Twice daily; DB = Double-blind; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 6 Number of Joints with Limited Range of Motion in Double-Blind and Open-Label Phases, Study 195*



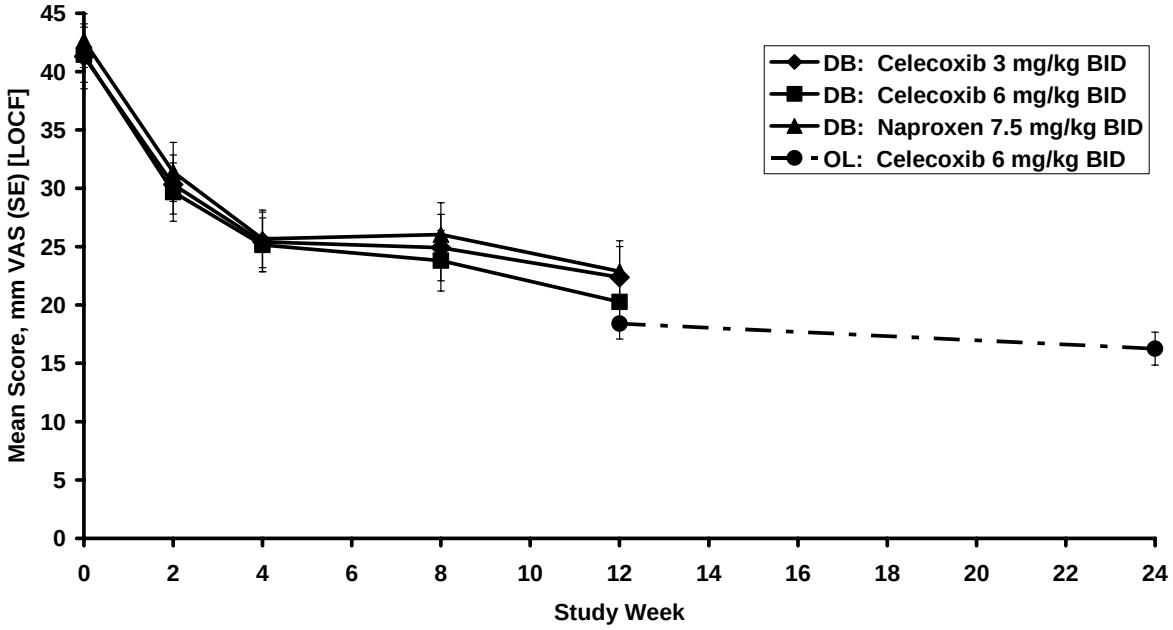
* ITT Population
BID = Twice daily; DB = Double-blind; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 7 Laboratory Marker of Inflammation (C-Reactive Protein, mg/L) in Double-Blind and Open-Label Phases, Study 195*



* ITT Population
BID = Twice daily; DB = Double-blind; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Figure 8 Parent's Assessment of Child's Arthritis Pain (100-mm VAS) in Double-Blind and Open-Label Phases, Study 195*



* ITT Population
BID = Twice daily; DB = Double-blind phase; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL = Open-label phase; VAS = Visual analog scale
NOTE: OL data were from 202 patients who completed the DB phase and entered the OL phase at Week 12.

Results in the open-label phase for the ACR Pediatric 30 core set measures (Table 7) demonstrated that the overall mean change from Weeks 12 to 24 for each of the measures was small. Analysis of results by double-blind treatment showed more favorable results for all measures (after 12 weeks of open-label treatment with celecoxib 6 mg/kg BID) in patients who received naproxen previously in the double-blind phase than in patients who received either dosage of celecoxib.

Table 7. Results in Open-Label Phase for ACR Pediatric 30 Core Set Measures by Treatment in Double-Blind Phase, Study 195*

Efficacy Measure / Statistic	Celecoxib 3 mg/kg BID in DB Phase N = 62	Celecoxib 6 mg/kg BID in DB Phase N = 70	Naproxen 7.5 mg/kg BID in DB Phase N = 70	Overall N = 202
Physician's Global Assessment of Disease Activity (100-mm VAS)[a]				
Week 12 mean (SE)[b]	17.60 (1.73)	15.86 (1.72)	14.99 (1.55)	16.09 (0.96)
Mean change, Week 12-24 (SE)	0.60 (1.98)	-1.40 (1.41)	-4.87 (1.38)	-1.99 (0.92)
Parent's Global Assessment of Overall Well-Being (100-mm VAS)[a]				
Week 12 mean (SE)[b]	18.40 (2.08)	17.98 (2.03)	21.13 (2.41)	19.20 (1.26)
Mean change, Week 12-24 (SE)	1.27 (2.94)	-1.08 (2.32)	-6.61 (2.26)	-2.27 (1.45)
Parent's Assessment of Physical Function (0-3 Numeric Scale)[a]				
Week 12 mean (SE)[b]	0.52 (0.07)	0.51 (0.07)	0.48 (0.06)	0.50 (0.04)
Mean change, Week 12-24 (SE)	-0.05 (0.04)	0.01 (0.03)	-0.06 (0.03)	-0.03 (0.02)
Number of Joints With Active Arthritis (73 Total Joints Assessed)				
Week 12 mean (SE)[b]	4.68 (1.04)	3.21 (0.53)	2.77 (0.57)	3.51 (0.42)
Mean change, Week 12-24 (SE)	-0.19 (0.43)	-0.07 (0.51)	-0.60 (0.42)	-0.29 (0.26)
Number of Joints With Limited Range of Motion (67 Total Joints Assessed)				
Week 12 mean (SE)[b]	4.71 (1.05)	3.89 (0.75)	2.87 (0.63)	3.79 (0.47)
Mean change, Week 12-24 (SE)	0.21 (0.52)	0.07 (0.41)	-0.50 (0.31)	-0.08 (0.24)
Laboratory Marker of Inflammation (C-Reactive Protein, mg/L)				
Week 12 mean (SE)[b]	10.50 (2.29)	12.52 (3.30)	10.68 (3.12)	11.26 (1.72)
Mean change, Week 12-24 (SE)	1.14 (2.31)	-0.23 (2.54)	-2.17 (2.02)	-0.48 (1.33)

* ITT Population; LOCF

ACR = American College of Rheumatology; BID = Twice daily; DB = Double blind; ITT = Intent-to-treat; LOCF = Last observation carried forward

[a] Higher scores indicate poorer well-being or function; negative mean changes indicate improvement.

[b] Last observation prior to the first dose of open-label study medication (baseline for open-label phase)

PedsQL™ scores improved in all treatment groups, with no statistically significant between-group differences. Overall, the improvements in least squares (LS) mean change from Baseline to Week 12 were greater for the celecoxib 6 mg/kg BID and naproxen 7.5 mg/kg BID treatment groups than the celecoxib 3 mg/kg BID treatment group.

As post-hoc exploratory analyses, the percentages of patients who met the ACR Pediatric 50 and ACR Pediatric 70 Response criteria at Week 12 were evaluated (ie, improvements of ≥50% and ≥70%, respectively, in ≥3 core set measures with >30% worsening in at most 1 core set measure). ACR Pediatric 50 Response rates were 56% for the celecoxib 3 mg/kg BID treatment group, 61% for celecoxib 6 mg/kg BID treatment group, and 55% for the naproxen 7.5 mg/kg BID treatment group. ACR Pediatric 70 Response rates were 25% for the celecoxib 3 mg/kg BID treatment group, 37% for the celecoxib 6 mg/kg BID treatment group, and 33 % for the naproxen 7.5 mg/kg BID treatment group. In both analyses, Week 12 results with both celecoxib dosages met the noninferiority criterion with respect to results with naproxen that was defined for the primary efficacy analysis.

7.4. Safety Results of Study 195

During the 12-week double-blind phase, most patients (≥87% by treatment group) received study medication for at least 60 days. In the 12-week open-label phase, 55% of patients received celecoxib 6 mg/kg BID for at least 85 days.

A total of 166 patients experienced treatment-emergent adverse events during the double-blind portion of the study (49 [63.6%] in the celecoxib 3 mg/kg BID treatment group, 57 [69.5%] in the celecoxib 6 mg/kg BID treatment group, and 60 [72.3%] in the naproxen 7.5 mg/kg BID treatment group). Table 8 provides an overview of the adverse events that occurred at a frequency of ≥5% in any treatment group during the double-blind portion of the study.

The types of adverse events reported most frequently were similar for all treatment groups. Overall, the greatest incidence of adverse events occurred in the GI and infections and infestations system organ classes. The most commonly occurring (≥5% of patients) adverse events for patients treated with celecoxib 3 mg/kg BID were coded to MedDRA terms representing headache (13.0%); upper abdominal pain and pyrexia (each 7.8%); nausea and cough (each 6.5%); and nasopharyngitis and diarrhea (each 5.2%). The most commonly occurring adverse events for patients treated with celecoxib 6 mg/kg BID were coded to MedDRA terms representing headache (9.8%); pyrexia (8.5%); arthralgia, abdominal pain and cough (each 7.3%); and upper abdominal pain, vomiting, and nasopharyngitis (each 6.1%). The most commonly occurring adverse events for patients treated with naproxen 7.5 mg/kg BID were coded to MedDRA terms representing headache (15.7%); nausea, vomiting, and pyrexia (each 10.8%); upper abdominal pain (9.6%); diarrhea and cough (8.4%); and abdominal pain and dizziness (each 7.2%).

Table 8. Incidence of Adverse Events Occurring in ≥5.0% of Patients in Any Treatment Group[a] in Decreasing Frequency (in the Celecoxib 6 mg/kg Treatment Group) Within a System Organ Class, Study 195*

System Organ Class[b] Adverse Event Preferred Term	Celecoxib 3 mg/kg BID (N = 77) n (%)		Celecoxib 6 mg/kg BID (N = 82) n (%)		Naproxen 7.5 mg/kg BID (N = 83) n (%)	
Any adverse event	49	(63.6)	57	(69.5)	60	(72.3)
Eye disorders	4	(5.2)	4	(4.9)	4	(4.8)
Gastrointestinal disorders	20	(26.0)	20	(24.4)	30	(36.1)
Abdominal pain NOS	3	(3.9)	6	(7.3)	6	(7.2)
Abdominal pain upper	6	(7.8)	5	(6.1)	8	(9.6)
Vomiting NOS	2	(2.6)	5	(6.1)	9	(10.8)
Diarrhoea NOS	4	(5.2)	3	(3.7)	7	(8.4)
Nausea	5	(6.5)	3	(3.7)	9	(10.8)
General disorders and administration site conditions	10	(13.0)	9	(11.0)	15	(18.1)
Pyrexia	6	(7.8)	7	(8.5)	9	(10.8)
Infections and infestations	19	(24.7)	16	(19.5)	22	(26.5)
Nasopharyngitis	4	(5.2)	5	(6.1)	4	(4.8)
Injury and poisoning	3	(3.9)	5	(6.1)	4	(4.8)
Investigations	2	(2.6)	9	(11.0)	6	(7.2)
Musculoskeletal, connective tissue & bone disorders	6	(7.8)	8	(9.8)	14	(16.9)
Arthralgia	2	(2.6)	6	(7.3)	3	(3.6)
Nervous system disorders	13	(16.9)	9	(11.0)	17	(20.5)
Headache NOS	10	(13.0)	8	(9.8)	13	(15.7)
Dizziness (exc vertigo)	1	(1.3)	1	(1.2)	6	(7.2)
Respiratory, thoracic and mediastinal disorders	6	(7.8)	12	(14.6)	12	(14.5)
Cough	5	(6.5)	6	(7.3)	7	(8.4)
Skin and subcutaneous tissue disorders	8	(10.4)	6	(7.3)	15	(18.1)

* ITT Population

Abbreviations: BID = Twice Daily, exc = Excluding; NOS = Not Otherwise Specified.

[a] Includes only adverse events that were reported up to 28 days after the last dose of study medication.

[b] If a patient had more than 1 adverse event within a system organ class, that patient is counted only once in the overall incidence for that system organ class.

GI disorders occurred more commonly in patients treated with naproxen than in patients treated with either celecoxib 3 mg/kg BID or celecoxib 6 mg/kg BID (36.1%, 26.0% and 24.4%, respectively). No consistent pattern of dose dependence was apparent for frequencies of GI disorders in celecoxib-treated patients. Skin and subcutaneous tissue disorders were also more frequently reported in patients treated with naproxen than in patients treated with either celecoxib 3 mg/kg BID or celecoxib 6 mg/kg BID (18.1%, 10.4%, and 7.3%, respectively). No celecoxib-treated patients experienced cardiovascular events or events representative of renal dysfunction during the double-blind trial. No fatal outcomes were reported.

During the open-label phase of the study, 96 (47.5%) of 202 patients treated with celecoxib 6 mg/kg BID experienced adverse events that were not present during the double-blind phase of the study. There was no increase in the overall incidence of adverse events relative to the double-blind phase of the study. As was observed during the double-blind phase of the study, the greatest incidence of adverse events occurred in the GI disorders and infections

and infestations system organ classes. No unexpected adverse events of clinical importance emerged. No fatal outcomes were reported during the open-label phase of the trial. One patient experienced inflammatory myopericarditis attributed to a flare of systemic features of JRA. There was no indication that the etiology of the chest pain was ischemic in nature; additionally, the patient's past medical history included myopericarditis.

Three patients (3.9%) in the celecoxib 3 mg/kg BID treatment group and 2 patients (2.4%) in the celecoxib 6 mg/kg BID treatment group experienced serious adverse events during the double-blind phase of the study (Table 9); no serious adverse events were reported in the naproxen treatment group. In the celecoxib 3 mg/kg BID treatment group, abdominal pain, acute cytomegalovirus hepatitis, and acute viral illness were reported as serious. In the celecoxib 6 mg/kg BID treatment group, exacerbations of JRA and asthma were reported as serious. Only the abdominal pain and exacerbation of asthma events were considered related to treatment. As shown in Table 9, 4 patients (2.0%) in the open-label phase (in which all patients were treated with celecoxib 6 mg/kg BID) experienced serious adverse events, none of which were considered related to celecoxib by the study investigators.

Table 9. Serious Adverse Events, Study 195*

Patient No.	Age (yr)/ Sex	Event Description: MedDRA Term (CRF Text)	Intensity	Time to Onset (Days)	Duration (Days)	Drug Related	Action Taken	Outcome
			Celecoxib 3 mg/kg BID					
01045	15.2 F	Abdominal pain NOS (Abdominal pain)	Severe	1	14	Yes	PW	Recovered
01303	11.3 M	Viral infection NOS (Acute Viral Illness)	Moderate	84	2	No	DDC	Recovered
01351	7.9 F	Hepatitis cytomegalovirus (Acute CMV hepatitis)	Moderate	29	6	No	PW	Recovered
			Celecoxib 6 mg/kg BID					
01176	6.7 M	Asthma NOS (Asthma)	Severe	1	6	Yes	PW	Recovered
01326	13.2 M	Juvenile rheumatoid arthritis (Worsening of juvenile rheumatoid arthritis)	Severe	57	1	No	PW	Recovered
			Celecoxib 6 mg/kg BID (Open-label Phase)					
01044[a]	15.6 M	Myopericarditis (Myopericarditis)	Severe	99	5	No	PW	Recovered
01088[b]	14.2 F	Abdominal pain upper (Epigastralgia)	Moderate	150	3	No	DDC	Recovered
		Non-accidental overdose (Overdose intentional)	Moderate	150	3	No	DDC	Recovered
		Vomiting NOS (Vomiting)	Mild	150	1	No	DDC	Recovered
01161[a]	12.0 M	Lower respiratory tract infection NOS (Lower tract respiratory infection)	Moderate	129	14	No	None	Recovered
01225[a]	7.7 F	Lymphadenopathy (Lymphadenopathy)	Severe	109	11	No	None	Recovered
		Pyrexia (Fever)	Severe	109	6	No	None	Recovered
		Sore throat NOS (Sored throat)	Severe	109	11	No	None	Recovered
		Torticollis (Torticollis)	Mild	109	6	No	None	Recovered

* ITT Population
BID = Twice Daily; CRF = Case Report Form; DDC = Study Drug Dose Delayed/Changed; MedDRA = Medical Dictionary for Regulatory Activities; NOS = Not Otherwise Specified; PW = Study Drug Permanently Withdrawn.
[a] Patient received celecoxib 6 mg/kg BID in the double-blind phase.
[b] Patient received celecoxib 3 mg/kg BID in the double-blind phase.

Overall, most of the reported serious adverse events were assessed by the investigators as not drug related (viral, cytomegalovirus, and lower respiratory tract infections; JRA exacerbation; myopericarditis; upper abdominal pain and vomiting with overdose;

lymphadenopathy, fever, sore throat, and torticollis), and the nature of these events does not suggest a causal association with celecoxib. Serious adverse events that were considered to be drug related were reported in 2 of the 9 patients (both events from the double-blind phase of the study) for whom any serious adverse events were reported. The reported serious adverse events considered drug related are mentioned in current product labeling: (Abdominal pain is listed as an adverse event previously reported in controlled arthritis trials, and a precaution states that celecoxib should be used with caution in patients with preexisting asthma). No dose dependence was observed for the frequency of serious adverse events during the double-blind phase. No pattern was apparent with respect to time of onset of serious adverse events.

The number of permanent discontinuations from the study due to adverse events was low. Thirteen patients withdrew from the study due to adverse events during the double-blind phase, including 3 patients (3.9%) in the celecoxib 3 mg/kg BID treatment group, 7 patients (8.5%) in the celecoxib 6 mg/kg BID treatment group, and 3 patients (3.6%) in the naproxen 7.5 mg/kg BID treatment group. The majority of discontinuations in the celecoxib 3 mg/kg BID treatment group and the naproxen 7.5 mg/kg BID treatment group were due to GI disorders; however, no patients in the celecoxib 6 mg/kg treatment group discontinued due to GI disorders. The most frequent type of adverse events leading to discontinuation in the celecoxib 6 mg/kg BID treatment group were abnormal laboratory findings (MedDRA terms representing hematuria, abnormal liver function tests, and increased transaminase), which did not lead to discontinuation in the other treatment groups. During the open-label phase, 3 patients experienced adverse events leading to permanent discontinuation from the study: 2 patients discontinued due to GI disorders, and the third patient discontinued due to allergic dermatitis.

There were no clinically relevant treatment differences between either dose of celecoxib and naproxen in the mean changes from Baseline to Week 12 in clinical laboratory measures of interest (Table 10, Table 11). Based on shift analyses, very few patients in any treatment group experienced shifts from normal values at Baseline to values either below normal for hemoglobin and hematocrit or above normal for aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), creatinine, or blood urea nitrogen (BUN) at Week 12/Final visit or, as a more conservative assessment, at any visit, during the double-blind portion of the study. (Criteria for relevant values above and below normal are provided in the footnotes of the tables.)

Table 10. Hematology Laboratory Results of Interest for Double-Blind Phase, Study 195*

Assay (Units)	Statistic	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
Hemoglobin (g/L)	No. patients assessed	71	75	77
	Baseline mean	123.2	123.5	123.6
	Mean change from baseline ± SE	-2.1±0.96	-1.2±0.95	-4.4±1.01*[6]
	Shift from normal value[a] at baseline to below normal value, n/N (%)			
	Week 12/Final visit	2/71 (2.8)	7/75 (9.3)	9/77 (11.7)
	Any visit	3/71 (4.2)	12/75 (16.0)	16/77 (20.8)
Hematocrit (fraction)	No. patients assessed	71	74	77
	Baseline mean	0.38	0.38	0.38
	Mean change from baseline ± SE	-0.003±0.003	-0.005±0.003	-0.013±0.003*[3]/*[6]
	Shift from normal value[b] at baseline to below normal value, n/N (%)			
	Week 12/Final visit	1/71 (1.4)	1/74 (1.4)	0/77 (0.0)
	Any visit	1/71 (1.4)	2/74 (2.7)	0/77 (0.0)

* ITT Population

BID = Twice daily; ITT = Intent-to-treat

*[3] $p<0.05$ versus celecoxib 3 mg/kg BID, from analysis of covariance using pairwise treatment comparisons with treatment group as a factor and baseline value as a covariate

*[6] $p<0.05$ versus celecoxib 6 mg/kg BID, from analysis of covariance using pairwise treatment comparisons with treatment group as a factor and baseline value as a covariate

[a] Normal hemoglobin (g/L): 2 years = 110-140; 3-5 years = 118-147 (females), 110-145 (males); 6-11 years = 112-155; ≥12 years = 116-164 (females), 127-181 (males)

[b] Normal hematocrit (fraction): All patients = 0.3-0.4

Table 11. Chemistry Laboratory Results of Interest for Double-Blind Phase, Study 195*

Assay (Units)	Statistic	Celecoxib 3 mg/kg BID	Celecoxib 6 mg/kg BID	Naproxen 7.5 mg/kg BID
AST (U/L)	No. patients assessed	71	79	79
	Baseline mean	25.2	25.0	26.5
	Mean change from baseline ± SE	3.1±2.36	1.7±0.98	-1.4±0.87
	Shift from normal value[a] at baseline to above normal value, n/N (%)			
	Week 12/Final visit	1/71 (1.4)	1/79 (1.3)	0/79 (0.0)
	Any visit	1/71 (1.4)	2/79 (2.5)	1/79 (1.3)
ALT (U/L)	No. patients assessed	73	80	80
	Baseline mean	16.5	16.2	17.2
	Mean change from baseline ± SE	3.3±2.84	2.0±2.19	-0.9±1.00
	Shift from normal value[b] at baseline to above normal value, n/N (%)			
	Week 12/Final visit	1/73 (1.4)	1/80 (1.3)	0/80 (0.0)
	Any visit	1/73 (1.4)	3/80 (3.8)	0/80 (0.0)
LDH (U/L)	No. patients assessed	68	77	79
	Baseline mean	196.2	198.1	200.3
	Mean change from baseline ± SE	4.8±6.34	5.6±3.39	-4.8±2.96
	Shift from normal value[c] at baseline to above normal value, n/N (%)			
	Week 12/Final visit	1/68 (1.5)	0/77 (0.0)	0/79 (0.0)
	Any visit	1/68 (1.5)	0/77 (0.0)	0/79 (0.0)
Creatinine (µmol/L)	No. patients assessed	73	80	81
	Baseline mean	39.9	39.3	40.5
	Mean change from baseline ± SE	-0.03±0.97	0.74±0.86	-0.60±0.80
	Shift from normal value[d] at baseline to above normal value, n/N (%)			
	Week 12/Final visit	0/73 (0.0)	0/80 (0.0)	0/81 (0.0)
	Any visit	0/73 (0.0)	0/80 (0.0)	0/81 (0.0)
BUN (mmol/L)	No. patients assessed	73	80	81
	Baseline mean	4.51	4.67	4.60
	Mean change from baseline ± SE	0.22±0.16	0.41±0.17	0.97±0.16**/***
	Shift from normal value[e] at baseline to above normal value, n/N (%)			
	Week 12/Final visit	1/73 (1.4)	0/80 (0.0)	3/81 (3.7)
	Any visit	1/73 (1.4)	1/80 (1.3)	9/81 (11.1)

* ITT Population

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BID = Twice daily; BUN = Blood urea nitrogen; ITT = Intent-to-treat; LDH = Lactic dehydrogenase

** $p<0.01$ versus celecoxib 6 mg/kg BID, from analysis of covariance using pairwise treatment comparisons with treatment group as a factor and baseline value as a covariate

***$p<0.001$ versus celecoxib 3 mg/kg BID, from analysis of covariance using pairwise treatment comparisons with treatment group as a factor and baseline value as a covariate

[a] Normal AST (U/L): All patients = ≤75

[b] Normal ALT (U/L): All patients = ≤75

[c] Normal LDH (U/L): All patients = ≤400

[d] Normal creatinine (µmol/L): 2-12 years = ≤92; ≥13 years = ≤110

[e] Normal BUN (mmol/L): All patients = ≤8.6

Analysis of sitting systolic blood pressure showed small mean increases from Baseline to Week 12 in all treatment groups (Table 12), with a somewhat larger increase in the naproxen treatment group (1.60 mmHg) than in the celecoxib treatment groups (0.76-0.91 mmHg); however, differences were not statistically significant. No consistent patterns were apparent in the percentages of patients with ≥15% increases in systolic blood pressure from Baseline to Week 12 or from Baseline to the maximum values measured in the study. Also observed were decreases of ≥15% in systolic blood pressure from Baseline to Week 12 and from Baseline to the minimum values measured in the study.

Table 12. Analysis of Sitting Systolic Blood Pressure, Study 195*

Statistic	Celecoxib 3 mg/kg BID N = 77	Celecoxib 6 mg/kg BID N = 82	Naproxen 7.5 mg/kg BID N = 83
Baseline mean, mmHg (SD)	99.3 (11.74)	101.3 (12.48)	101.9 (13.12)
LS mean change from Baseline to Week 12 (SE) [a]	0.91 (1.09)	0.76 (1.06)	1.60 (1.05)
P value versus naproxen [a]	0.6493	0.5703	--
Patients with ≥15% increases from Baseline, n/N (%)[b]			
To Week 12	7/73 (9.6)	5/80 (6.3)	11/83 (13.3)
To maximum value measured in study	16/73 (21.9)	10/80 (12.5)	15/83 (18.1)
Patients with ≥15% decreases from Baseline, n/N (%)[b]			
To Week 12	5/73 (6.8)	2/80 (2.5)	1/83 (1.2)
To minimum value measured in study	10/73 (13.7)	8/80 (10.0)	13/83 (15.7)

* ITT Population
BID = Twice daily; ITT = Intent-to-treat; LS = Least squares
[a] From analysis of covariance model with treatment group as a factor and baseline value, gender, age and height as covariates, and using last observation carried forward for missing data
[b] Observed cases

Overall, safety-related analyses of laboratory values and vital signs during the double-blind phase of the study did not indicate remarkable differences between the 3 treatment groups. Results of analyses of laboratory values and vital signs during the open-label phase of the study were consistent with those observed during the double-blind phase.

Physical developmental effects were assessed by analyses of mean changes from Baseline in weight and height and of frequencies of extreme weight values. No significant differences between treatment groups were observed in these analyses during the double-blind phase of the study. No developmental delays or losses of developmental milestones were reported as adverse events from developmental histories.

Slit-lamp eye examinations were performed at Screening and at Weeks 12 and 24 to assess for the presence of uveitis, and adverse events consistent with uveitis were analyzed. During the double-blind phase of the study, frequencies of slit-lamp examination results considered abnormal and clinically relevant were lower in both celecoxib treatment groups (1.8% and 3.3%) than in the naproxen treatment group (5.1%). Frequencies of adverse events consistent with uveitis (including uveitis, corneal opacity, blurred vision, eye disorder, anterior chamber disorder, and eye inflammation) were similar among treatment groups. Results of these assessments during the open-label phase of the study were similar to those observed in celecoxib-treated patients during the double-blind phase.

Four patients (5.2%) in the celecoxib 3 mg/kg BID treatment group, 10 patients (12.2%) in the celecoxib 6 mg/kg BID treatment group, and 8 patients (9.6%) in the naproxen 7.5 mg/kg BID treatment group were observed to have had systemic onset of JRA, but with currently inactive systemic features, at the time of randomization (Table 4). Only 1 patient with systemic-onset JRA (described above in the discussion of adverse events during the open-label phase) experienced a definite flare of systemic features (myopericarditis) during the course of the study; however, the patient had a past history of myopericarditis, and the investigator did not consider the systemic flare to be related to treatment with celecoxib.

In addition to monitoring of safety by the Sponsor's study personnel, a DSMB convened at the Agency's request conducted 2 unblinded assessments of the available double-blind safety data while the open-label phase of the study was still ongoing (the double-blind phase of the study had already completed). The DSMB recommended that the open-label phase of the study continue as planned following each review.

7.5. Conclusions

The results of Study 195 showed that celecoxib at dosages of 3 or 6 mg/kg BID is as efficacious as an approved dosage of naproxen in the symptomatic treatment of JRA. Safety and tolerability with both celecoxib dosages were similar to naproxen, with trends toward better safety/tolerability with respect to GI and skin-related adverse events.

8. GENERAL SAFETY OF CELECOXIB IN ADULTS WITH RHEUMATOID ARTHRITIS

By means of comparison to safety data from Study 195, safety data for celecoxib in an adult population with RA are provided by an integrated analysis of 2 randomized, double-blind, placebo- and active-controlled studies. The 2250 patients in this integrated RA population were grouped into the following treatment groups for analysis: placebo (452 patients); celecoxib 100, 200, and 400 mg BID (468, 453, and 434 patients, respectively); celecoxib any dose (all 1355 patients receiving celecoxib); and naproxen 500 mg BID (443 patients). The overall exposure to study medication was 232.1 patient-years in the celecoxib any dose treatment group.

The overall frequency of adverse events was higher in celecoxib-treated patients (61.7%) and in NSAID-treated patients (63.0%) than in placebo-treated patients (53.5%); this pattern was also observed for most of the most frequently reported (≥1%) adverse events in celecoxib-treated patients (Table 13). The most commonly reported adverse event in all patients in the integrated analysis was headache, for which the frequency in the celecoxib any dose treatment group (14.8%) was lower than that in the placebo treatment group (20.4%) and higher than that in the naproxen 500 mg BID treatment group (12.9%). Of the 6 most common adverse events experienced by celecoxib-treated and NSAID-treated patients, 3 of the adverse events were GI-related (dyspepsia, diarrhea, nausea).

In summary, this analysis of 2 clinical trials in adult RA suggests an overall safety and tolerability profile of celecoxib that is similar to naproxen.

Table 13 Adverse Events Reported in ≥1% of Celecoxib-Treated Patients by Decreasing Frequency, Integrated Adult Rheumatoid Arthritis Studies*

	Number (Percentage) of Patients					
Adverse Event (MedDRA)	**Placebo N = 452**	**Celecoxib 100 mg BID N = 468**	**Celecoxib 200 mg BID N = 453**	**Celecoxib 400 mg BID N = 434**	**Celecoxib Any Dose N = 1355**	**Naproxen 500 mg BID N = 443**
Any adverse event	**242 (53.5)**	**293 (62.6)**	**274 (60.5)**	**269 (62.0)**	**836 (61.7)**	**279 (63.0)**
Headache	92 (20.4)	70 (15.0)	72 (15.9)	59 (13.6)	201 (14.8)	57 (12.9)
Dyspepsia	26 (5.8)	42 (9.0)	36 (7.9)	36 (8.3)	114 (8.4)	48 (10.8)
Diarrhoea	16 (3.5)	25 (5.3)	24 (5.3)	27 (6.2)	76 (5.6)	17 (3.8)
Upper respiratory tract infection	21 (4.6)	29 (6.2)	21 (4.6)	16 (3.7)	66 (4.9)	27 (6.1)
Nausea	23 (5.1)	18 (3.8)	15 (3.3)	17 (3.9)	50 (3.7)	17 (3.8)
Nasopharyngitis	15 (3.3)	13 (2.8)	19 (4.2)	16 (3.7)	48 (3.5)	22 (5.0)
Sinusitis	12 (2.7)	17 (3.6)	16 (3.5)	13 (3.0)	46 (3.4)	13 (2.9)
Rash	10 (2.2)	12 (2.6)	20 (4.4)	13 (3.0)	45 (3.3)	7 (1.6)
Cough	6 (1.3)	9 (1.9)	14 (3.1)	12 (2.8)	35 (2.6)	5 (1.1)
Insomnia	6 (1.3)	9 (1.9)	11 (2.4)	11 (2.5)	31 (2.3)	13 (2.9)
Sinus headache	12 (2.7)	9 (1.9)	8 (1.8)	13 (3.0)	30 (2.2)	4 (0.9)
Sinus congestion	5 (1.1)	10 (2.1)	13 (2.9)	5 (1.2)	28 (2.1)	7 (1.6)
Back pain	17 (3.8)	12 (2.6)	11 (2.4)	4 (0.9)	27 (2.0)	4 (0.9)
Influenza-like illness	5 (1.1)	7 (1.5)	8 (1.8)	10 (2.3)	25 (1.8)	5 (1.1)
Pharyngolaryngeal pain	3 (0.7)	10 (2.1)	8 (1.8)	7 (1.6)	25 (1.8)	5 (1.1)
Flatulence	1 (0.2)	10 (2.1)	8 (1.8)	6 (1.4)	24 (1.8)	4 (0.9)
Dizziness	10 (2.2)	6 (1.3)	9 (2.0)	9 (2.1)	24 (1.8)	15 (3.4)
Pruritus	4 (0.9)	11 (2.4)	3 (0.7)	10 (2.3)	24 (1.8)	4 (0.9)
Bronchitis	9 (2.0)	7 (1.5)	5 (1.1)	11 (2.5)	23 (1.7)	5 (1.1)
Abdominal pain upper	5 (1.1)	7 (1.5)	9 (2.0)	6 (1.4)	22 (1.6)	11 (2.5)
Urinary tract infection	4 (0.9)	8 (1.7)	5 (1.1)	9 (2.1)	22 (1.6)	7 (1.6)
Oedema peripheral	3 (0.7)	5 (1.1)	7 (1.5)	9 (2.1)	21 (1.5)	6 (1.4)
Muscle spasms	5 (1.1)	9 (1.9)	6 (1.3)	5 (1.2)	20 (1.5)	5 (1.1)
Myalgia	10 (2.2)	8 (1.7)	5 (1.1)	6 (1.4)	19 (1.4)	4 (0.9)
Vomiting	5 (1.1)	4 (0.9)	4 (0.9)	10 (2.3)	18 (1.3)	6 (1.4)
Constipation	12 (2.7)	7 (1.5)	7 (1.5)	3 (0.7)	17 (1.3)	13 (2.9)
Abdominal pain	6 (1.3)	7 (1.5)	2 (0.4)	6 (1.4)	15 (1.1)	6 (1.4)
Seasonal allergy	0 (0.0)	6 (1.3)	5 (1.1)	4 (0.9)	15 (1.1)	1 (0.2)
Arthralgia	2 (0.4)	6 (1.3)	5 (1.1)	4 (0.9)	15 (1.1)	2 (0.5)

* ITT Population
BID = Twice daily; MedDRA = Medical Dictionary for Regulatory Affairs

9. OTHER RELEVANT SAFETY INFORMATION

In addition to the findings from Study 195 and adult RA data presented above, demonstrating a similar adverse event profile with celecoxib relative to naproxen, a review of available data was performed by the Sponsor to identify other potential risks which cannot be excluded based solely on the results of Study 195. Of note, specific emphasis was placed on rare adverse events, adverse events related to prolonged therapy, unexpected adverse events associated with other drugs in this class, and developmental aspects. Further data were assessed for adverse events of interest relevant to children given the known adverse effect

profile of nonselective NSAIDs in adults, specifically gastrointestinal tolerability. Serious cardiovascular adverse events in childhood are extremely rare; however, hypertension is increasingly recognized in childhood, therefore review of available cardiovascular and cardiorenal data was performed. In summary, these data together provide evidence that celecoxib is not associated with unique safety concerns compared to nonselective NSAIDs used in treating JRA.

This was assessed by review of data from the following sources:

- Non-clinical data
- Postmarketing data on exposure from non-approved uses in children
- Data from clinical studies of celecoxib in adults:
  - Arthritis conditions
  - Prevention of sporadic adenomatous polyposis

The following conclusions could be drawn from this review:

- Non-clinical data suggest a potential role for COX-2 in renal development and in the central nervous system. Extensive animal testing, however, has demonstrated no evidence for adverse effects on development in growing juvenile animals with celecoxib.
- Spontaneous reports of adverse events from children do not provide evidence for a different safety profile to adult use of celecoxib.
- In a meta-analysis of randomized trials in adult OA and RA patients, celecoxib is associated with a significantly improved GI safety and tolerability profile compared to nonselective NSAIDs.
- In one of two long-term placebo-controlled chemoprevention trials in adults, celecoxib was associated with significantly increased risk of serious cardiovascular events (cardiovascular death, nonfatal myocardial infarction [MI], and non-fatal stroke) compared to placebo. In another similar trial, celecoxib was not associated with a significantly increased risk of serious cardiovascular events.
- In a meta-analysis of >41,000 adult patients from randomized controlled trials across multiple indications, celecoxib was not associated with significantly increased risk for serious cardiovascular events compared to nonselective NSAIDs.
- Observational trials have not demonstrated increased risk for serious cardiovascular events with celecoxib compared to nonselective NSAIDs.
- In a meta-analysis of randomized controlled trials in adult arthritis patients, celecoxib use was associated with hypertension or aggravated hypertension at a similar rate to NSAIDs.

- In a prospective trial designed to assess blood pressure effects between celecoxib and naproxen in adults, no significant differences were observed.

9.1. Nonclinical Safety Studies of Celecoxib

9.1.1. Cyclooxygenase Expression During Development

The enzyme COX-1 is widely found in nearly all tissues under basal conditions, which suggests highly conserved physiological function. Most importantly, it is constitutively expressed in the platelets, blood vessels, GI tract, brain, and kidney.[72, 73, 74, 75] COX-2 generally is not detectable or only barely detectable in normal cells, including cells associated with inflammation; however, it is constitutively expressed in the kidney, brain, and tissues of the reproductive tract.[72, 76, 77, 78, 79] In kidney, brain, and male reproductive tract, COX-2 can be developmentally regulated.

In contrast to adult human kidney, abundant COX-2 expression is reported during the perinatal period in human kidney.[77, 80, 81, 82] The renal system, however, is considered mature in human juvenile ≥2 years thus potential effect of COX-2 inhibition in these patients is considered similar to adults.

Both COX-1 and COX-2 are constitutively expressed in the brain and are localized primarily to neurons. Both enzymes are shown to be developmentally regulated in the brains of animals,[83, 84, 76] and COX-2 activity coincides with the final stages of brain maturation.

Temporal expression of COX-2 has been reported in male rats during sexual maturation.[79]

9.1.2. Nonclinical Safety Assessment of Celecoxib in Juvenile Rats and Dogs

A nonclinical safety assessment was completed for celecoxib in juvenile animals. Toxicology studies were conducted in juvenile rats and juvenile dogs during periods that correlate with human ages 2 to 18 years. In addition to standard toxicology endpoints, special assessments were conducted to evaluate any effects on general body growth and development.

9.1.2.1. Study in Juvenile Rats

Celecoxib was administered orally at doses of 10 to 80 mg/kg/day once daily to immature rats for at least 7 weeks, beginning on postnatal Day 7. No effects on growth or neurobehavioral development were seen at any dose level. The major toxic effect observed was gastrointestinal tract injury as seen previously in adult rats. Effects related to obstruction and dilatation of testicular tubules, along with other abnormalities in the rat testis, were observed in celecoxib-treated juvenile male rats. These effects did not have any impact on adult fertility and, importantly, these effects were not seen in other animal models (dogs) with anatomy similar to human testis. Due to the unique anatomy of the rat, this was considered specific to juvenile rats and not relevant to humans.

9.1.2.2. Study in Juvenile Dogs

Celecoxib was administered orally twice daily at total doses of 15 to 50 mg/kg/day by capsule to juvenile dogs beginning at 10 weeks of age for at least 5 months. There were no direct toxicities observed at any dose, and treatment with celecoxib had no apparent effect on growth or development. Transient septic skin sores were noted at 35 and 50 mg/kg/day dose groups. Such skin sores are also seen commonly with non-selective NSAIDs in dogs. Of note, the immature dogs appeared less susceptible to the GI toxicity of celecoxib than their adult counterparts. No GI toxicity was seen in juvenile animals at the 50 mg/kg/dose while this dose resulted in GI ulceration and mortality in adult dogs.

9.1.2.3. Summary of Nonclinical Safety of Celecoxib

In conclusion, all toxicities seen in juvenile animals are similar to those previously observed in adult animals, and toxicities did not occur either at greater rates or at lower celecoxib systemic exposures in juvenile animals relative to adults. The exception, testicular abnormalities, was limited to the rat and not seen in other species. Celecoxib had no effects on either growth or development in either juvenile rats or juvenile dogs. There were no significant effects of human relevance in juvenile animals at exposures at least 4- to 8-fold greater than the exposure associated with recommended daily doses in humans.

9.2. Postmarketing Data from Sponsor's Safety Database

This section summarizes adverse events in children exposed to celecoxib (including possible exposure in utero and exposure due to breast-feeding) that have been reported and entered into the Sponsor's safety database.

Overall, a total of 203 cases have been reported from 31 December 1998 through 15 March 2006; no new or unique safety concerns are evident from spontaneous reporting.

Data are available from the Sponsor's safety database, including the following:

- **Spontaneous cases:** Cases from health care professionals, including those provided by health authorities and literature sources, that contain serious adverse events and nonserious unlisted (ie, not cited in prescribing information at the time the case was processed) adverse events; cases with serious or nonserious unlisted adverse events received from consumers and/or legal services are included only if follow-up information is received from a health care professional. (Since the spontaneous reporting system is a voluntary adverse-event reporting system, the data are not necessarily complete and may include unsubstantiated diagnoses and sparse information despite follow-up attempts made by Pfizer.)

- **Cases reported from clinical studies (of any sponsorship):** Cases containing serious adverse events that are assessed as having a reasonable possibility of a causal relationship with the study drug by the investigator or the sponsor

- **Solicited cases:** Cases from Pfizer-sponsored marketing programs that originated or received follow-up information from a health care professional that contain serious

adverse events assessed by the reporter or by Pfizer as having a reasonable possibility of a causal relationship with the subject drug

A search of the Pfizer safety database was conducted, encompassing the period from 31 December 1998 through 15 March 2006, with this cutoff date chosen to enable inclusion of search results in the JRA sNDA. Cumulatively over this period, there were 203 cases (involving 359 events) reported involving children (where age was reported as ≤16 years, or the patient was described as newborn, neonate, infant, child, adolescent, or teenager by the reporter), representing 0.3% of all cases.

Of the 187 cases reporting gender, there were 105 females and 82 males. The ages of the patients ranged from 0.5 to 16 years (mean = 10 years). There were 170 spontaneously reported cases, 13 cases reported by health authorities, 1 case reported through literature, and 19 clinical study cases. Fifty-five cases were assessed as serious and 148 were classified as nonserious.

Table 14 compares the reporting rates of events seen in >2% of the 203 pediatric celecoxib cases with the reporting rates of these events seen in all 60,072 celecoxib cases added to the Pfizer safety database in the specified time period.

Table 14. Comparison of Celecoxib Pediatric Case Events (with Reporting Rate >2%) to All Celecoxib Case Events

MedDRA System Organ Class Preferred Term	Number of Pediatric Cases (%)[a]	Total Number of All Cases (%)[b]
Gastrointestinal disorders		
Abdominal pain	6 (3.0%)	1,725 (2.9%)
Nausea	5 (2.5%)	2,029 (3.4%)
Vomiting	13 (6.4%)	891 (1.5%)
General disorders and administration site conditions		
Drug ineffective	7 (3.4%)	7,199 (12.0%)
No adverse effect[c]	19 (9.4%)	360 (0.6%)
Injury, poisoning and procedural complications		
Accidental exposure	20 (9.9%)	33 (0.1%)
Drug administration error	14 (6.9%)	100 (0.2%)
Drug exposure during pregnancy	11 (5.4%)	141 (0.2%)
Drug exposure via breast milk	5 (2.5%)	7 (<0.1%)
Overdose	9 (4.4%)	51 (0.1%)
Nervous system disorders		
Dizziness	6 (3.0%)	1,912 (3.2%)
Headache	5 (2.5%)	1,577 (2.6%)
Somnolence	5 (2.5%)	681 (1.1%)
Pregnancy, puerperium and perinatal conditions		
Normal newborn	5 (2.5%)	15 (<0.1%)
Skin and subcutaneous tissue disorders		
Pruritus	6 (3.0%)	1,715 (2.9%)
Rash	7 (3.4%)	4,022 (6.7%)
Urticaria	5 (2.5%)	1,368 (2.3%)

MedDRA = Medical Dictionary for Regulatory Activities

[a] Percentages expressed as a proportion of the total of 203 pediatric celecoxib cases.

[b] Percentages expressed as a proportion of the total of 60,072 celecoxib cases.

[c] Term applied mainly to cases involving accidental or indirect exposure to celecoxib, in which no adverse events were observed.

Higher reporting rates for pediatric cases are to be expected for accidental exposure, drug administration error, drug exposure during pregnancy, drug exposure via breast milk, overdose, and normal newborn. (Note that the total number of cases reported as "normal newborn" [in the Total Number of All Cases column of the table above] are likely to include mothers receiving celecoxib who delivered normal newborns.) These findings are not unexpected, as children are more likely to take medication that is left unattended or to take medication incorrectly. Children are indirectly exposed during pregnancy or via breast milk due to their mother's use of celecoxib.

Compared to adult cases, reporting rates were similar between abdominal pain, dizziness, headache, pruritus, and urticaria. There was a higher reporting rate of vomiting and somnolence in pediatric patients, while there was a lower reporting rate of nausea, drug ineffectiveness, and rash. The reporting rate for cases categorized as no adverse effect was higher in the pediatric population because most of these cases involved accidental or indirect exposure to celecoxib, in which no adverse events were observed.

Review of all the pediatric cases identified 7 cases of unlabeled, serious events for which no alternate etiologies or contributory factors were reported: 1) upper intestinal occlusion (in an infant breast-fed while the mother was taking celecoxib; patient recovered); 2) suicide; 3) seizure or syncopal episode (patient recovered); 4) low calcium reading (after ingesting 25 to 30 celecoxib capsules; no outcome information provided); 5) pulmonary infiltrates (no outcome information provided); 6) breathlessness and trembling (events abated at an unknown time); 7) dehydration, fever, lethargy, loss of appetite, herpes zoster, and a "mild heart murmur" (outcome unknown at the time of the report).

The pediatric cases were also reviewed for events of special concern for safety surveillance of celecoxib usage, including SCAR and thromboembolic cardiovascular events. No new safety concerns were raised.

Through review of results from a survey of pediatric rheumatologists after the cut-off date of 15 March 2006, the Sponsor is aware of one additional cardiovascular event, that of pulmonary embolus, described in Section 9.3.

Five fatal cases have been reported: 1 report contained insufficient information for a proper assessment, and alternate causes of death were reported in the other 4 cases (1 case of aneurysm rupture, 3 cases of cancer progression).

An updated review of the Pfizer safety database, covering the period of 16 March 2006 through 31 August 2006, identified 14 additional celecoxib cases (involving 40 events) involving children. This review did not reveal any new safety concerns regarding the use of celecoxib.

In summary, review of the spontaneously reported cases in pediatric patients does not reveal any new or unique safety concerns regarding the use of celecoxib in this patient group.

9.3. Survey of Pediatric Rheumatologists

Following the withdrawal of Vioxx® (rofecoxib) from markets worldwide, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), an association of pediatric rheumatologists in the US and Canada, surveyed its members in January 2005 to gather information on vascular complications associated with the use of celecoxib and naproxen in JRA patients. The rheumatologists surveyed were asked about their awareness of any JRA patient receiving either drug who experienced any thrombotic event such as stroke, myocardial infarction, pulmonary embolism, and deep venous thrombosis (excluding patients with coexistent vasculitis or a known hypercoagulative state) over their practice careers. Since it was considered unlikely that accurate data could be obtained on the total numbers of JRA patients ever treated with specific drugs by the survey participants, data on length of practice in pediatric rheumatology were also collected to provide indirect information on extent of exposure. Of 130 rheumatologists surveyed, 95 responded (73%), representing a total of 1546 years of practice in pediatric rheumatology (mean of 16.3 years). Although no events were reported for the JRA population, one thrombotic event reported was a case of pulmonary embolism reported for a 16-year-old female who was receiving celecoxib 200 mg BID for a possible diagnosis of psoriatic arthritis. This patient's complicated medical history

and concomitant medication use were likely contributing factors to the event; however, the association of celecoxib cannot be excluded.

9.4. Pertinent Safety Results from Celecoxib Studies in Adults

9.4.1. Gastrointestinal Tolerability and Safety

Review of the literature reveals numerous clinical trials assessing GI safety and tolerability of celecoxib in adults. Of note, Moore et al[85] conducted a systematic review and meta-analysis of randomized, double-blind, controlled trials of 2 weeks duration or longer with any dose of celecoxib and any comparator, in OA or RA. Data from thirty-one Phase 2- 4 clinical trial reports of celecoxib in OA or RA were evaluated.

The 31 trials had 39,605 patients who were randomized and received at least one dose of study medication (intention-to treat population). Of these, 25,903 had OA, 3,232 had RA, and 10,470 were in trials including patients with both conditions.

Discontinuations due to adverse events or discontinuations due to GI-related adverse events were statistically significantly less frequent with celecoxib compared to NSAIDs. Further, GI adverse events were reported significantly less frequently with celecoxib compared to NSAIDs. Specific GI adverse events of abdominal pain, dyspepsia, and vomiting were also reported significantly less frequently with celecoxib compared to NSAIDs. The meta-analysis also demonstrated significantly decreased risk for anemia, GI ulcer detected by endoscopy, and clinical ulcers and GI hemorrhage in this adult population.

Notwithstanding the above, all NSAIDs, including celecoxib, are labeled with a boxed warning that they may be associated with increased GI risk.

9.4.2. Cardiovascular Safety

The current celecoxib US package insert includes preliminary safety data from The Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial. This trial, along with the similar Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial, was conducted to assess the efficacy and safety of celecoxib compared to placebo in the prevention of sporadic adenomatous colorectal polyps in adults.

The results of a follow-up adjudication of serious adverse events over the entire 3-year core period of both the APC trial and the PreSAP trial have recently been published. The results demonstrated a statistically significant, dose-dependent increase in risk for serious cardiovascular events (non-fatal MI, non-fatal stroke, cardiovascular death) with celecoxib treatment compared to placebo treatment in the APC trial, but not the PreSAP trial. In parallel, celecoxib treatment was associated with statistically significant, dose-dependent increases in mean systolic and diastolic blood pressure compared to treatment with placebo in the APC trial, but no such increase was observed in the PreSAP trial.

Harmonized language and boxed warnings for all NSAIDs that they may be associated with increased cardiovascular risk was included in labeling for the NSAID class as whole in 2005.

Of note, however, is that significantly increased cardiovascular risk with celecoxib, at any dose, has not been observed compared to nonselective NSAIDs, either in randomized controlled trials or epidemiologic datasets. In a meta-analysis of 39 randomized studies encompassing over 41,000 patients, analyses of cardiovascular events (non-fatal MI, non fatal stroke, cardiovascular death, assessed independently in a blinded manner by a 3-member Endpoint Committee) did not demonstrate significantly increased risk with celecoxib ≥200 mg total daily dose (TDD) compared to nonselective NSAIDs.[86]

In addition to the analysis above, a review of the epidemiology literature and a meta-analysis was conducted by Harvard School of Public Health and the Spanish Center for Pharmacoepidemiological Research (CEIFE) in cooperation with Pfizer, to evaluate cardiovascular safety in clinical practice in relation to use of both nonselective NSAIDs and selective COX-2 inhibitors.[87] Sixteen studies published between 2000 to 2005 were selected for inclusion in the meta-analysis. Across all studies, over 3.5 million people were included from 4 cohort studies, 9 nested case-control and 3 case-control studies.

Evidence from the 16 studies included in this review shows that on average there is a 10% increase in risk of MI among users of nonselective NSAIDs, with noticeable variability among individual agents. Compared with no NSAID use, neither celecoxib nor naproxen were associated with significantly increased risk.

Notwithstanding the above, all NSAIDs, including celecoxib, are currently labeled with a boxed warning that they may be associated with increased cardiovascular risk.

9.4.3. Cardio-Renal Safety Data for Celecoxib: Adult Arthritis Data

Cardiovascular thromboembolic events are extremely rare in childhood and most likely associated with severe dislipidemic or hypercoagulable states. Hypertension, however, is increasingly recognized as a condition in childhood.

Data regarding cardio-renal outcomes (increased creatinine, adverse events of hypertension or aggravated hypertension) are available from the published systematic review and meta-analysis by Moore.[85] In this analysis, increased creatinine (>1.3 times upper limit of normal) in adult arthritis patients was reported similarly for celecoxib and nonselective NSAIDs, and further there were no significant differences reported for adverse events of hypertension or aggravated hypertension. Sowers et al[88] evaluated blood pressure effects of celecoxib and naproxen in adult OA patients with Type II diabetes and hypertension (treated with either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). There were 404 patients randomized in a double-blind, double–dummy, parallel-group study to celecoxib 200 mg QD, rofecoxib 25 mg QD or naproxen 500 mg BID for 12 weeks of treatment. Blood pressure was rigorously assessed with 24-hour ambulatory monitoring at Baseline, Week 6, and Week 12. For the primary endpoint of the trial, mean 24-hour systolic blood pressure, there were no significant differences between celecoxib and naproxen at either Week 6 or Week 12.

In summary, in both meta-analyses of adult arthritis trials; and in a prospective randomized clinical trial utilizing robust methodology, there is no evidence for increased risk of cardio-

renal adverse events or effects on blood pressure with celecoxib compared to nonselective NSAIDs and specifically naproxen.

10. COMPARISON OF PEDIATRIC CLINICAL SAFETY DATA AND OTHER RELEVANT SAFETY DATA, AND OVERALL SAFETY CONCLUSIONS

Safety results of Study 195 were consistent with effects that could be predicted from nonclinical studies of celecoxib in juvenile animals (Section 9.1.2). No growth or physical developmental effects were apparent in celecoxib-treated patients relative to naproxen-treated patients. GI disorders were the most frequently reported class of adverse events.

The types of adverse events reported most frequently by celecoxib-treated patients were comparable in Study 195 and the integrated adult RA population. Of the most commonly reported individual adverse events in Study 195 (Table 8), all but pyrexia were also among the most frequent events in celecoxib-treated adult RA patients (Table 13). In Study 195 and in the adult RA population, GI adverse events were some of the most frequently reported types of adverse events and were generally more frequent in naproxen-treated patients than in celecoxib-treated patients. In adult populations, there is a significantly improved GI tolerability profile with celecoxib compared to nonselective NSAID use. Although Study 195 was not designed to evaluate GI tolerability, the results are consistent with adult experience. The imbalance between celecoxib- and naproxen-treated patients in favor of celecoxib-treated patients for frequencies of skin-related adverse events that was observed in Study 195 was not apparent in the adult RA population. In adult RA, skin-related adverse events were reported more frequently with celecoxib compared to naproxen. This imbalance might be exaggerated by the small sample size in Study 195, since the higher overall frequency of skin-related adverse events in naproxen-treated patients relative to celecoxib-treated patients appeared to reflect a number of diverse individual adverse events. Skin-related adverse events were also reported with higher frequency with naproxen compared to rofecoxib in a similar trial to Study 195.[24] Spontaneous reports of skin-related adverse events accounted for a similar or lower percentage of overall reports from children compared to adults. No instances of SCAR have been reported to the Sponsor from the use of celecoxib in children. SCAR events have been reported with all NSAIDs, including celecoxib, in adults and can be fatal. Further, SCAR has been reported in children with NSAIDs other than celecoxib such as ibuprofen. The absence of reports does not exclude the risk of SCAR with celecoxib in children; however, there is no evidence that, if present, this risk is greater than with other NSAIDs.

The sample size in Study 195 was inadequate to detect adverse events at the low frequencies (generally <2%) observed for thromboembolic cardiovascular events and renal adverse events in the adult RA population and for the cardiovascular outcomes assessed in the long-term adult studies. It would be expected that occurrence of thromboembolic cardiovascular events would be far less likely in Study 195 than in these adult populations regardless of sample size considerations. Serious cardiovascular thromboembolic events are extremely rare in childhood and generally associated with severe dyslipidemic or hypercoagulable states.

Hypertension is, however, increasingly recognized as being relevant in pediatric care and is now second in prevalence only to obesity and asthma among chronic conditions in children,

affecting around 4% of school age children.[45] The clear association of adult hypertension and long-term cardiovascular morbidity and mortality, together with the association of NSAIDs as a class of drugs with hypertension, is relevant to the treatment of JRA with NSAIDs. Data from controlled trials in adults have not demonstrated increased risk for hypertension or aggravated hypertension with celecoxib compared to nonselective NSAIDs. Specifically, effects on systolic blood pressure were similar between celecoxib and naproxen. Study 195 was not designed to evaluate blood pressure in a rigorous manner; however, effects in this trial were consistent between celecoxib and naproxen and with the experience in adults. There is no evidence for a greater effect on blood pressure control in pediatric patients with celecoxib than with naproxen. As a result, if present, long-term sequelae of disturbing blood pressure control in childhood on adult cardiovascular outcomes would be expected to be similar between celecoxib and nonselective NSAIDs such as naproxen.

The relatively short duration of Study 195 is a further limiting factor for detection of rare events or events occurring only after extended treatment. It is not possible to conclusively state that celecoxib is without long-term developmental effects, or long-term effects on growth beyond 6 months of treatment. Nonclinical tests in animals, however, do not support that any such effects are present.

Based on nonclinical data with celecoxib, the available clinical data from Study 195, clinical experience from postmarketing surveillance of unapproved pediatric use, and adult experience, the safety profile of celecoxib appears similar to that of other NSAIDs in the JRA population and specifically naproxen.

11. PEDIATRIC DOSING OF CELECOXIB

This section summarizes the rationale and data supporting dosing of children to achieve similar exposures as those achieved in Study 195. Study 195 demonstrated that celecoxib 3 and 6 mg/kg BID administered to children and adolescents 2 to <17 years of age, using an investigational suspension formulation, was efficacious (non-inferior) and safe when compared with naproxen 7.5 mg/kg BID in treating the signs and symptoms of JRA. Prior to and during the conduct of Study 195, the Sponsor investigated the development of 4 different dosage forms to meet the needs of pediatric patients and others who are unable to swallow an intact capsule. Three of these dosage forms were extensively investigated from a pharmaceutical perspective and included an oral suspension, an orally disintegrating tablet, and a chewable tablet. None of these 3 formulations were determined to be suitable for commercialization in a timely manner due to technical difficulties. Therefore, the Sponsor proposed to the Agency discontinuing the development of these formulations and undertook to evaluate the current capsule formulations studied in adults.

The rationale behind selection of capsule doses that could be used by children was based on achieving peak plasma concentrations (termed Cmax) that do not exceed those observed in Study 195 using the suspension (termed the safety boundary), while achieving a similar overall exposure (area under the curve [AUC] from 0 to 12 hours, or AUC[0-12]) to those that resulted in the non-inferiority of celecoxib to naproxen in Study 195 (termed the efficacy boundary).

The capsule PK profiles and capsule doses for children were derived by integrating population PK results from Study 195 along with historical adult capsule data and taking into account observed differences in absorption between the suspension and capsule formulations. Of note was a 15% lower AUC and approximately 50% lower Cmax for the suspension relative to the capsule in a relative bioavailability study in healthy adults. PK data from Study 195 suggest that weight influences celecoxib clearance to a much lesser extent than was originally assumed in the dosing scheme employed in Study 195 (a 10 kg patient is predicted to have 40% lower oral clearance (not adjusted for weight) compared with a 70 kg adult).

The outcome of this approach is that similar exposures as those achieved in Study 195 with the suspension can be achieved with capsule dosing in children with a 50-mg BID dose for those weighing 10-25 kg and a 100-mg BID dose for those weighing >25 kg (Table 15).

This approach is consistent with principles outlined in the FDA guidance for the translation of results from controlled efficacy and safety trial (Study 195) from one dose, or dosage form (oral suspension) to a new dose, or dosage form (capsules) using PK data.[89]

Table 15 Comparison of Suspension and Derived Capsule Dosing Regimens for JRA

Dosing Regimen Employed in Study 195	**Weight Category→**	**9-12 kg**	**13-25 kg**	**26-37 kg**	**38-50 kg**	**>50 kg**
	Suspension (3 mg/kg BID)	25 mg BID	50 mg BID	75 mg BID	100 mg BID	150 mg BID
	Suspension (6 mg/kg BID)	50 mg BID	100 mg BID	150 mg BID	200 mg BID	300 mg BID
Derived Dosing Regimen	**Weight Category→**	**10 - 25 kg**		**>25 kg**		
	Capsule[a]	50 mg BID		100 mg BID		

[a] Administered either intact or sprinkled on applesauce

The estimated mean steady-state Cmax and AUC(0-12) values for the suspension doses in Study 195 and the predicted values for the proposed capsule doses are summarized in Table 16 for body weights that represent the categories used for dosing in Study 195.

Table 16 Mean Steady-State Cmax and AUC(0-12) Estimates from Study 195 and Those Predicted for the Derived Capsule Doses

	Cmax (ng/mL)			**AUC(0-12) (ng•h/mL)**		
Weight (kg)	**Suspension 3 mg/kg BID**	**Suspension 6 mg/kg BID**	**Capsule[a]**	**Suspension 3 mg/kg BID**	**Suspension 6 mg/kg BID**	**Capsule[a]**
10	120	241	415	1030	2059	2603
13	220	440	380	1921	3842	2428
25	178	356	305	1616	3232	2041
26	263	527	530	2399	4798	4036
38	311	622	466	2893	5786	3650
50	285	570	424	2690	5380	3394

[a] 50 mg BID capsule doses for weight ranging from 10 kg to 25 kg and 100 mg BID capsule doses for weight >25 kg

As shown in Table 16, for the majority of weight groups, the predicted Cmax for capsule doses does not exceed the suspension Cmax values (safety boundary) in Study 195 while AUC(0-12) estimates are within those for the 3 mg/kg and 6 mg/kg dose groups in Study 195 (efficacy boundary). The exception is in the case of a patient weighing 10 kg, where the capsule Cmax and AUC(0-12) values are predicted to be approximately 70% and 25% greater than those of the 6 mg/kg dose group in Study 195. However, these exposures are less than those in adults following administration of 100 mg BID capsule (Cmax of 454 ng/mL; AUC(0-12) of 3577 ng•h/ml).

It is recognized that some children will not be able to swallow an intact capsule. For these children, the Sponsor investigated the alternative administration method of emptying the contents of a celecoxib capsule onto a small amount (teaspoon) of applesauce (capsule sprinkles) for ingestion. This is an accepted method for oral administration of chemically compatible drugs to children (eg, as described in prescribing information for omeprazole[90]). Since celecoxib does not exhibit a characteristic taste, the capsule contents are ideally suited to be delivered as a sprinkle dosage form. A relative bioavailability study was performed to compare the bioavailability of celecoxib sprinkled on applesauce to that of the intact capsule in healthy adults. Study results showed that the 2 methods produced similar AUC and Cmax values, demonstrating the suitability of capsule sprinkles for those who are unable to swallow an intact capsule. The "sprinkle" capsule formulation proposal was agreed by the Agency with the stipulation to conduct appropriate in-use stability studies, as the sprinkled capsule contents may not be delivered immediately after preparation. The results of these in-use studies indicate that celecoxib capsules, either 50 or 100 mg, may be sprinkled onto a variety of applesauces. The product may be used immediately following sprinkling onto applesauce. Additionally, the applesauce that is sprinkled with capsule contents may be stored at either room temperature or in the refrigerator for up to 6 hours.

In conclusion, given the unavailability of the suspension formulation used in Study 195, a capsule dosing methodology was derived. The use of capsules, administered intact or as sprinkles (50 mg BID for patients weighing 10-25 kg and 100 mg BID for those weighing >25 kg) would provide similar systemic exposures of celecoxib as those observed in Study 195.

12. ENHANCED PHARMACOVIGILANCE

The safety profile of any pharmaceutical compound reflects an evolving body of knowledge extending from preclinical investigations to the first use of the compound in humans and throughout the post-approval life cycle of the product. Pfizer has established postmarketing surveillance operations and has also evolved a pharmacovigilance and risk management process that is comprised of several components.

In order to continue to monitor the safety profile of celecoxib as it may relate to the pediatric population, analysis and interpretation of safety observations are required through enhanced pharmacovigilance, including monitoring data as they emerge from ongoing clinical trials.

Pfizer reviews all adverse event reports collected from multiple sources (postmarketing surveillance, population-based registries, and safety information from ongoing clinical

studies), with particular emphasis on the adequacy of the information and whether additional information is required to evaluate the event(s) in the context of the disease under treatment, concurrent disease, and concomitant medications. For adverse events of special interest, such as cardiovascular events or SCAR, Pfizer has generated Data Capture Aids (targeted questionnaires) for more aggressive follow-up of particular events of concern in order to ensure complete and timely collection of data from spontaneously reported cases. The Data Capture Aid is developed for selected areas of interest and is a tool that helps with systematic collection and more accurate characterization of the reported events. It also provides additional lines of inquiry resulting in a significant improvement in the quality of information captured.

Pfizer has also established dedicated, product specific Pharmacovigilance Core Working Groups and Risk Management Committees as the cornerstone of the pharmacovigilance and risk management process. These committees are comprised of a variety of safety stakeholders that, in addition to safety and risk management expertise, represent regulatory, medical and clinical expertise. The Pharmacovigilance Core Working Group conducts periodic review of adverse events of interest and the Risk Management Committee develops and updates risk management plans (as necessary), in order to ensure that commitments made are executed.

12.1. Long-Term Evaluation During Ongoing Clinical Studies

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) study will define the relative cardiovascular risk of celecoxib in adults over a minimum 18-month treatment period. The data will be assessed to determine if information may be related back to the pediatric population. Increasing data are directly linking disturbance of blood pressure with adverse cardiovascular outcomes with all NSAIDs, though this is yet to be conclusively proven. PRECISION will also evaluate (as a secondary measure) effects on blood pressure and renal function. These measures may be more directly applicable to the pediatric population.

Furthermore, any additional information from future adult or pediatric studies of celecoxib will also be evaluated.

12.2. Independent Expert Dermatology Panel

An independent panel of dermatology experts was commissioned in July 2002 for the primary purpose of performing periodic review and medical assessment of spontaneous reports of SCAR received by Pfizer for COX-2 medications. Since July 2002, the panel has reviewed, assessed, and adjudicated all cases of SCAR for celecoxib. The panel has also been involved with review of case validation comments of SCAR cases reported for selective COX-2 inhibitors as well as providing consultation with respect to labeling updates and other regulatory inquiries. With respect to use of celecoxib in the pediatric population, the panel will continue to fulfill their role and responsibilities.

12.3. Risk Evaluation

As regular assessments of safety data are made, pharmacovigilance and risk management methods will be revisited to determine if a greater effort is needed to maximize patient safety or if a potential issue is no longer considered a risk that requires management.

13. CONCLUSION ON BENEFIT AND RISK

JRA is a serious illness in children with limited treatment options. Pain and inflammation are common in all types of JRA; they may persist over time and may be present even with the most efficacious DMARD treatments. Treatment of pain and inflammation is an important component of medical care for JRA, both from a fundamental ethical perspective and for mitigation of adverse functional outcomes associated with higher levels of pain experienced by children. NSAIDs are currently one of the preferred first-line drug therapies for all types of JRA, and are the mainstay of treatment of signs and symptoms. However, the few NSAIDs approved for children all inhibit both COX-1 and COX-2 at therapeutic doses and are associated with frequent GI adverse events in the JRA population; little or no information is available on their long-term safety in pediatric use. Given its distinct mode of action, the availability of information for celecoxib in the treatment of JRA expands knowledge on the range of therapeutic options, offering the potential advantage of greater GI tolerability relative to nonselective NSAIDs. A drug with better GI tolerability than naproxen might be expected to have a similar advantage over other NSAIDs used in the treatment of JRA. Use of celecoxib in the treatment of JRA has been reported, suggesting the need for information guiding its use through appropriate labeling.

The results discussed in this document indicate that celecoxib is an appropriate treatment option for children with JRA with a favorable risk-benefit profile. In Study 195, celecoxib showed efficacy comparable to that attained with an approved dosage of naproxen, with some trending toward improved GI tolerability. Comparison of the safety results of Study 195 with relevant nonclinical and adult clinical safety data, along with safety information on pediatric use of celecoxib from sources other than clinical studies (eg, spontaneous reporting), did not suggest substantial differences between the pediatric and the known adult safety profiles of celecoxib.

Celecoxib has been shown to be well tolerated and efficacious in patients with pauciarticular and polyarticular course JRA, including in those patients with systemic onset JRA with persistent arthritis but currently inactive systemic features. In Study 195, both celecoxib dosages tested met the primary objective of non-inferiority to naproxen with respect to the ACR Pediatric 30 Response. This validated instrument assesses response to therapy on 6 core variables including pain, function and disease activity. In general, no statistically significant nor clinically relevant differences between either celecoxib treatment group and the naproxen treatment group were observed for any of the component assessments of the ACR Pediatric 30 Response. Furthermore, effects on treating the signs and symptoms of JRA were observed with celecoxib from the first assessment after 2 weeks of treatment and were maintained through to 12 weeks. In the further 12-week, open-label extension phase of the study, response to celecoxib was durable as evidenced by similar efficacy results after 6 months of treatment to those observed after 12 weeks of treatment.

Safety results of Study 195 suggested a favorable safety profile for both celecoxib dosages relative to naproxen, with numerically lower frequencies of adverse events overall and of GI and skin disorders. Although serious adverse events were reported only for celecoxib-treated patients, no dose dependence was observed for the frequency of serious adverse events. The reported serious adverse events represented a range of body systems and etiologies and could be considered typical of serious adverse events seen in children with JRA. Most of the reported serious adverse events were not considered drug related; the types of serious adverse events reported as drug related were consistent with product labeling. The overall frequencies of adverse events leading to discontinuation in the celecoxib treatment groups suggested possible dose dependence, but no consistent pattern was apparent in the types of adverse events leading to discontinuation. No celecoxib-treated patients experienced cardiovascular or cardiorenal events during the double-blind phase of the trial, and no fatal outcomes were reported. No substantial differences between treatment groups were observed for clinical laboratory results, vital signs, measures of physical developmental effects, or rates of systemic flare or uveitis flare. Of 22 patients with systemic-onset JRA (with inactive systemic features at baseline), only 1 (who received celecoxib 6 mg/kg BID during both phases of the study) experienced a definite flare of systemic disease during the course of the study.

The safety results of Study 195 were consistent with those that could be predicted based on nonclinical studies of celecoxib in juvenile animals, and were generally comparable to those observed in studies of adult RA patients with dosages of celecoxib similar to or higher than the dosages used in Study 195 (after correction for patient weight). Safety information on pediatric use of celecoxib from sources other than clinical studies (including spontaneous reporting) revealed no unexpected findings and was consistent with the known safety profile of celecoxib in adults.

Increased risk for serious cardiovascular events with celecoxib has been observed in one of two long-term placebo-controlled chemoprevention trials in adults; however, increased risk with celecoxib in adults compared to other nonselective NSAIDs has not been demonstrated in randomized or observational studies encompassing multiple indications. Serious cardiovascular outcomes are extremely rare in childhood, and in general related to severe dyslipidemic or hypercoagulable states. Hypertension is, however, increasingly recognized as affecting around 4% of children and is second in prevalence only to obesity and asthma among chronic medical conditions in childhood. Both selective and nonselective NSAIDs may exacerbate underlying hypertension, which may be more pertinent than serious cardiovascular events in children. JRA and the need for NSAID therapy extend into young adulthood for approximately 40%-50% of patients. However, the latent effects of disturbing blood pressure control with NSAIDs in childhood are unknown. All available data, however, point to the conclusion that celecoxib has a similar profile for disturbance of blood pressure compared with other NSAIDs. The association in adulthood of hypertension and long-term cardiovascular morbidity and mortality is not disputed.

In summary, the results of Study 195, along with other available data, suggest that the benefit:risk balance for celecoxib in the treatment of JRA is favorable within the confines of the available data. The available data, however, cannot exclude rare or latent effects.

Compared to similar studies, including those with other NSAIDs, Study 195 is of similar magnitude and duration to exclude a certain level of risk. Available diagnosis data suggest that celecoxib is currently being prescribed to children with JRA in the absence of labeling. Therefore, it is important to provide physicians with information that may guide dosing and administration and relevant safety information needed to help protect patient safety.

In conclusion, recognizing the balance between the need for providing new therapies to patients with JRA and the potential for unknown risk, this briefing document, further to the sNDA, is supportive of appropriate labeling with respect to the use of celecoxib in the pediatric population, ranging from the inclusion of safety information and pharmacokinetic data, through to full approval of the indication to treat symptoms of JRA. Of great importance to the Sponsor is our ethical responsibility to make appropriate information available to guide prescribing decisions for children.

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