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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

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8:00 a.m.

Gaithersburg Hilton
Gaithersburg, Maryland

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Robert Meyer, M.D.
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Sharon Hertz, M.D.
Jeffrey Siegel, M.D.
Carolyn Yancey, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. BATHON: I am Joan Bathon. I am Acting Chair for our meeting today and I would like to welcome all of the committee members and guests and attendees to this FDA Arthritis Advisory Committee meeting this morning to evaluate the risks and benefits of celecoxib for the treatment of juvenile arthritis.

I am going to go through a couple of housekeeping announcements and then we will introduce everyone around the table before we get started. First of all, to use the microphone, for those of you sitting at the table, press the button to talk and when you are done, please, turn it off so we don't get interference. Also, I am going to ask you to turn all of your cell phones off. Also, laptops must be off because we are getting some interference with the sound system. So, cell phones off; laptops off.

If you want to ask a question, please get eye contact with Johanna Clifford and she will put

your name down on a list. We are going to hold questions till the end of the presentation, unless they are extremely urgent, and then we will ask them at that point.

So, if we could start maybe at this far end of the table, and briefly state your name, your affiliation and your area of expertise, please.

DR. MCLESKEY: Charlie McLeskey. I am an anesthesiologist by training and I am employed by ZARS Pharma, a small drug development company in Salt Lake City, and I am here as the industry rep.

DR. SANDBORG: My name is Christy Sandborg. I am a pediatric rheumatologist at Stanford.

DR. GORMAN: Richard Gorman, pediatrician in private practice in Ellicott City, Maryland.

DR. DAUM: Good morning. I am Robert Daum. I am a pediatric infectious disease guy at the University of Chicago.

DR. PROSCHAN: I am Mike Proschan. I am a statistician from NIH. I have been with two different institutes, formerly NHLBI and now NIAID.

MS. DOKKEN: I am Deborah Dokken. I am a

family patient representative who serves on the Pediatric Advisory Committee, and currently Associate Director of a project called Initiative for Pediatric Palliative Care.

MR. LEVIN: Arthur Levin, Center for Medical Consumers, in New York. I am a member of the Drug Safety and Risk Management Committee and am here as the acting consumer representative.

DR. WEISE: I am Kathryn Weise. I am a practicing pediatric intensivist and bioethics consultant, Vice Chair of the Ethics Committee at the Cleveland Clinic Foundation, in Cleveland.

DR. MORRIS: Lou Morris, psychologist by training, and member of the Drug Safety and Risk Management Advisory Committee.

DR. HOLMBOE: I am Eric Holmboe. I am currently Vice President for Evaluation Quality Research at the American Board of Internal Medicine, and a member of the DSRM Committee.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the Arthritis Advisory Committee, FDA.

DR. CHESNEY: I am Joan Chesney. I am a

professor of pediatric infectious diseases at the University of Tennessee, in Memphis, and also Director of the Academic Programs Office at St. Jude Children's Research Hospital.

DR. LEHMAN: Tom Lehman. I am Chief of the Division of Pediatric Rheumatology at the Hospital for Special Surgery and the Cornell Campus of New York Presbyterian Hospital in Manhattan.

DR. O'NEIL: I am Kathleen O'Neil, from the University of Oklahoma. I am an associate professor of pediatrics and a pediatric rheumatologist.

DR. DAVIS: I am John Davis, associate professor of medicine at the University of California, San Francisco, and Director of the Division of Rheumatology Clinical Trial Center, and a member of the Arthritis Advisory Panel.

DR. BOULWARE: I am Dennis Boulware, an adult rheumatologist, professor of medicine, University of Alabama at Birmingham. I am on the Arthritis Advisory Committee.

DR. YANCEY: Carolyn Yancey, medical

officer in the Division of anesthesia, Analgesia and Rheumatology and a pediatric rheumatologist.

DR. SIEGEL: Jeffrey Siegel, clinical team leader in the Rheumatology Division, DAARP, at the FDA.

DR. HERTZ: Sharon Hertz, Deputy Director of the Division of Anesthesia, Analgesia and Rheumatology Drug Products.

DR. RAPPAPORT: Bob Rappaport, Division Director for DAARP.

DR. MEYER: I am Bob Meyer. I am the Director of the Office of Drug Evaluation II under which DAARP resides. DR. BATHON: Thank you, and I should also mention that Dr. Dennis Turk is here by phone. He is professor of anesthesiology at the University of Washington. Do we have Dr. Turk on the line?

DR. TURK: Yes, I am here. Thank you.

DR. BATHON: Great. Johanna Clifford will be presenting the conflict of interest next.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement

addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

The matter coming before the Arthritis Drugs Advisory Committee is a particular matter involving specific parties. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions.

In accordance with 18 USC 208(b)(3), full waivers have been granted to the following participants: Dr. Dennis Turk has been granted a waiver for his unrelated consulting and unrelated advisory board activity for two competing firms. He receives less than $10,001 per year from each firm.

Dr. Louis Morris has been granted a waiver for his unrelated consulting for two competing firms. He receives less than $10,001 per year from

each firm. In addition, Dr. Morris has been granted a waiver for his services as an expert witness on an unrelated matter for a law firm representing a competing firm. The fee is greater than $50,000 per year.

DR. Thomas Lehman has been granted a waiver for his unrelated speaker's bureau activities for two competing firms. He receives less than $10,001 per year from each firm.

DR. Joan Bathon has been granted a waiver for her unrelated consulting for a competing firm. She receives less than $10,001 per year.

Dr. Christy Sandborg has been granted a waiver for her spouse's unrelated consulting for a competing firm. Her spouse receives less than $10,001 per year.

In addition, Dr. Patricia Chesney has been granted waivers under 18 USC 208(b)(3) and 21 USC 344(n)(4) of the Food and Drug Modernization Act for ownership of stocks. The first is in a competing firm, valued at less than $5,001 and the second is in the sponsor, valued between $25,001 to

$50,000.

Waiver documents are available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Further, with respect to FDA's invited industry representative, we would like to disclose that Dr. Charles McLeskey is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. McLeskey's role on this committee is to represent industry interests in general and not any one particular company. Dr. McLeskey is an employee of ZARS Pharma.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. BATHON: Thanks, Johanna. Next we will turn to Bob Rappaport for some opening remarks. He is Director of the Division of Anesthesia, Analgesia and Rheumatology Products at CDER, FDA.

Opening Remarks

DR. RAPPAPORT: Good morning, everybody. Dr. Bathon, members of the committee, invited guests, I would like to thank you for your participation in this important meeting of the Arthritis Advisory Committee.

Today we will be discussing the risks and benefits associated with the use of Celebrex in pediatric patients with juvenile rheumatoid arthritis. The addition of a new indication to the Celebrex label, particularly an indication for

pediatric patients, raises many questions for the agency considering the apparent cardiovascular toxicity seen in adult patients treated with COX-2 inhibitory drug products specifically and all NSAID drug products in general.

As such, it is essential that in making a determination regarding the approvability of Pfizer's application for this new indication the concerns regarding the potential for cardiovascular toxicity in children with JRA be carefully considered, and that these concerns be assessed in concert with the available data on the efficacy of the product for this indication in addition to the other toxicities associated with this class of drugs.

Your discussion and recommendations will be invaluable to us as we proceed with our final assessment of this application. This morning you will hear a number of presentations from the agency as well as presentations by speakers representing the sponsor. These presentations will begin with a summary of the clinical profile of JRA and the

available treatments for this often devastating disease by Dr. Carolyn Yancey, a pediatric rheumatologist in our division.

Following Dr. Yancey's presentation, Dr. Sharon Hertz, one of our deputy directors, will discuss our current knowledge of the cardiovascular toxicity of the COX-2 selective inhibitory and other NSAID drug products.

A series of speakers from Pfizer, Drs. Giannini, Gold, Koch, Lovell and Stern, will then summarize the data from the clinical trials submitted in support of the request for approval of the JRA indication.

Finally, Dr. Jeffrey Siegel, our medical team leader for the rheumatology drug and biologic products, will summarize the available data on the efficacy and safety of Celebrex for the treatment of JRA, and the risks and benefits that must be addressed in order for us to make a final determination on the approvability of this new indication.

Following the morning break you will hear

from members of the community during the open public hearing portion of this meeting. We extend our thanks to those patients' families and advocates who took their time to come in today and provide personal testimony and additional insights to the committee and the agency.

This afternoon we have set aside additional time for you to ask questions of the speakers, the sponsor and the agency. From there, we will move on to the discussion points and questions prepared for you by the Division.

We are grateful for this opportunity to receive your input as experts in a number of disciplines that clearly have insights into the need for new treatments for JRA patients, the appropriate and safe use of these products in this population, and the implications of the efficacy and safety data that are available from the clinical trials performed by the sponsor, and of the known and unknown cardiovascular risks that might exist for these particularly vulnerable children.

Again, thank you for taking your time out of your busy schedules to participate in this process. Your discussion and recommendations will be a crucial component in our evaluation.

DR. BATHON: Thanks, Dr. Rappaport. We will proceed now to Dr. Yancey's presentation, introduction of JRA and the state of the art treatment armamentarium.

FDA Presentation

Introduction of Juvenile Rheumatoid Arthritis and Sate of the Art Treatment Armamentarium

DR. YANCEY: Good morning.

[Slide]

I am going to talk to you this morning about juvenile rheumatoid arthritis. This is a condition for which the Celebrex supplement has been submitted to the agency.

[Slide]

The agenda that I will go through this morning will begin with a discussion about the epidemiology, pathogenesis and etiology of juvenile rheumatoid arthritis. I will speak about the

classification of this condition and the clinical manifestations. I will discuss in detail the disease course, as well as the prognosis as we understand it now, and then conclude with a discussion about the treatment of juvenile rheumatoid arthritis and the state-of-the-art treatment armamentarium.

[Slide]

Just for clarification, chronic arthritis in childhood, characterized as juvenile rheumatoid arthritis, abbreviated as JRA, specifically refers to children who are less than 16 years of age. This definition also is consistent with the agency's definition of pediatrics.

[Slide]

The epidemiology of JRA: Overall the prevalence of juvenile rheumatoid arthritis is estimated to be from 30 to 150 per 100,000 children. If we consider the United States and Canada, there are an estimated 30,000 to 60,000 children and adolescents with JRA.

[Slide]

The pathogenesis and etiology of JRA are certainly multi-factorial. I will speak this morning about genetic considerations, hormonal as well as immunologic. The pathogenesis is characterized by chronic inflammation of the synovium. There is presence of articular cartilage damage that follows chronic inflammation. This, in many situations, is accompanied by extra-articular systemic manifestations.

The heterogeneity of JRA is fascinating without any doubt. There are at least three primary onset types of JRA, specifically pauciarticular, oligoarticular; polyarticular; and systemic. I will speak to these different types further into the presentation.

[Slide]

The genetic considerations: The basis of immune distinction between self and non-self is the major histocompatibility complex, MHC, that in humans is called the human leukocyte antigen. The HLA system comprises a family of polymorphic genes located on the short arm of chromosome number 6.

The polymorphisms of JRA suggest a non-mendelian inheritance. I will speak more to that when I talk specifically about the different subtypes.

The hormonal considerations have been fascinating when we look at the onset of JRA and the different peaks we see in different age groups. The differences in the sex ratio of JRA by subtype are clear. There are different peaks in pre-adolescents. We can also see peaks in post-adolescents, depending on what type of JRA onset we are speaking of.

[Slide]

In terms of the immune mechanisms, this area has probably received the greatest amount of attention. The disease process involves loss of tolerance towards auto-antigens which, in turn, will cause a chronic synovitis. There is production of numerous auto-antibodies and I am just going to list some of the major ones this morning:

Anti-nuclear antibodies, ANA, for example, are associated with the increased risk of

iridocyclitis, which is the inflammation in the anterior chamber of he eye. Rheumatoid factors: Auto-antibodies directed against the Fc fragment of IgG associated with about 10 percent of polyarticular JRA. Complement activation by circulating immune complexes may also contribute to the overall disease process.

[Slide]

Cytokines as well act on the immune system and other cells to initiate and sustain inflammation. The intercellular mediators, interleukin-1, IL-1, IL-6 and tumor necrosis factor-alpha are just a few, to name some. The immunomodulatory cytokines are produced by the T cells, interferon gamma, IL-4 and IL-2. Research certainly demonstrates that there are many more that are being discovered.

[Slide]

The classification of JRA was first established by the American College of Rheumatology, abbreviated as ACR. This actually took place in 1977.

[Slide]

This is the classification that the supplement has worked with. First, the age of onset, as I mentioned before, is less than 16 years of age. Arthritis is described as swelling or effusion or the presence of 2 or more of the following signs: Limitation of range of motion; tenderness or pain on motion; and increased heat in one or more joints. The duration of disease must be greater than or equal to 6 weeks.

The onset type is defined by the type of disease in the first 6 months. As I mentioned earlier, oligoarticular disease, also called pauciarticular JRA, is less than 5 inflamed joints. Polyarticular JRA is greater than or equal to 5 inflamed joints. Systemic onset JRA includes arthritis but with the characteristic fever.

Exclusion is very important. Exclusion of other forms of childhood arthritis is critical. Infectious diseases can mimic JRA. Malignancies can certainly mimic JRA and immune deficiencies.

[Slide]

These four photographs give you examples of what the disease can look like. In the youngster, on your left, you can see there is involvement of the small joints of the hand. There is also involvement of the wrist that you can see at the top.

This youngster, here, has systemic JRA involvement of small joints as well as large joints, and has typical muscle wasting proximal to that knee as well as distal to the knee.

The youngster here, in the left-hand corner, is a little boy who has pauciarticular JRA and is clearly struggling with involvement of his right knee.

The picture of the eye is a schema which demonstrates the inflammation that can occur in the anterior chamber of the eye, and I will speak to the consequences of this shortly.

[Slide]

JRA by type of onset: These are the three types of JRA by onset. If you look at the percent of cases, pauciarticular occurs in about 60 percent

of all cases of juvenile rheumatoid arthritis, polyarticular in approximately 30 percent, and systemic in 10 percent. The girl to boy ratio is different. In pauciarticular there is a 5:1 ratio of girls to boys. For polyarticular it is 3:1 and in systemic it is equal.

I have already mentioned the joint involvement. Systemic is the one condition in which it is variable. The age of onset in pauciarticular tends to be in our youngest children, early childhood, with a peak between approximately 1 and 2 years of age. Polyarticular disease is throughout childhood, with also a young peak. Systemic disease can occur throughout childhood and there is no peak for this involvement. The systemic involvement differs significantly. In pauciarticular the main involvement in these children is the uveitis. In polyarticular it can be mild or remitting systemic findings, or it can be significant articular involvement. The systemic symptoms, the fever and the rash can be self-limited, whereas, the chronic,

destructive arthritis can be unremitting in almost 50 percent of thee children.

The ANA is highest in the pauciarticular group. The vast majority of these children to have a positive ANA. In polyarticular disease we carefully look for rheumatoid factor positivity because these children tend to have a more aggressive course. The ANA in the polyarticular group is approximately 40-50 percent. In systemic there is much less production of these typical auto-antibodies. About 10 percent of these children have a positive ANA.

The prognosis differs by onset type. Pauciarticular children have a much better articular prognosis for the most part. Their eyesight though can be a very devastating outcome. Polyarticular disease has a guarded prognosis, moderately good; and systemic can be moderate to poor, and I will speak more about this later.

[Slide]

The extra-articular manifestations of JRA are demonstrated on this slide. I would direct

your attention particularly to the systemic condition where 100 percent of these children have fever. As you can see, this onset type has the greatest amount of extra-articular manifestations, rheumatoid rash, rheumatoid nodules, hepatosplenomegaly, pleuritis, as well as cardiovascular involvement, pericarditis as well as other cardiovascular complications.

[Slide]

The prognosis of JRA has come a long way. We understand a lot more about the severity of the disease. In pauciarticular JRA, for example, boys may be affected in older childhood or adolescence. We have actually learned that this may be a manifestation of an early spondyloarthropathy.

Leg length discrepancies from asymmetric knee synovitis and bone growth can cause flexion contractures, gait abnormalities and long-term growth abnormalities in these children.

The eye involvement, as I mentioned earlier, can actually lead to scarring or blindness anywhere from 15-20 percent in these children.

Active arthritis into adulthood, we now understand, can be as high as 40-50 percent in the pauciarticular type. Radiographic joint damage, specifically x-ray documentation, can be seen within five years.

[Slide]

When we consider polyarticular and systemic JRA, the active arthritis into adulthood is higher in both these conditions. It can be anywhere from 50-70 percent. Long-term disabilities occur in 30-40 percent of these children. Through studies that have been completed, there has been documentation on unemployment from 25-50 percent of adult JRA patients. Once a young person receives a diagnosis of JRA, as they mature into adulthood, they retain this diagnosis. Radiographic joint damage is seen within 2 years in this group. If you notice, this is much earlier x-ray damage of their joints. The mortality rates, specifically greater in the systemic condition, can be anywhere from 0.4 to 2 percent.

[Slide]

Let's shift now and talk about the treatment approach to JRA. Before the 1990s we saw pediatric rheumatologists use a very traditional pyramid approach, if you will, with the base being non-steroidal anti-inflammatory drugs. Intra-articular or oral corticosteroids were used. Disease-modifying anti-rheumatic drugs and, lastly, cytotoxic agents.

[Slide]

The evolving treatment has certainly seen a more aggressive course. The trend in managing JRA is much more aggressive treatment earlier in the disease course with the goal of preventing joint damage and slowing progressive articular damage.

[Slide]

I am going to go through the treatments that are available for JRA by category. Non-selective NSAIDs, those that have indications for this condition are aspirin, tolmetin sodium, ibuprofen and naproxen. I will focus on naproxen

because this is the NSAID that is most frequently used by pediatric rheumatologists.

The formulation is as a tablet and as a suspension, and this is indicated for children with JRA greater than 2 years of age at doses as you see. The adverse events are as you see them on the slide. The most common adverse events with this medication are gastrointestinal, central nervous system, particularly headaches in children, and rash.

[Slide]

The non-selective NSAIDs, COX-2 selective inhibitors, MOBIC, meloxicam, available as tablets and suspension, indicated specifically for pauciarticular and polyarticular course of JRA in children 2 years and older. The dose is as you see it. The adverse events again are most prominently gastrointestinal experiences, headache and increased incidence of infection. Pyrexia, as you see on this slide, is also very common in this class of drugs.

Vioxx, rofecoxib, available as tablets and

suspension, was withdrawn from the global market in September of 2004. The reason for that voluntary withdrawal was because of cardiovascular serious adverse events, specifically thromboembolic events, myocardial infarction and cerebral vascular accidents in adult patients. It is indicated for the relief of the signs and symptoms of JRA, again, in children 2 years and older.

[Slide]

Corticosteroids are still used. They are used for uncontrolled or life-threatening systemic disease. They are also used for the chronic uveitis that I spoke about, particularly with the pauciarticular children.

Intra-articular steroids are used for 1 or 2 joints that are recalcitrant to treatment, particularly in the pauciarticular category and in polyarticular disease. There are other forms of steroids, the intravenous form used for severe symptoms of systemic disease. Pediatric rheumatologists certainly seek to use the lowest dose of prednisone possible. Adverse events for

corticosteroids are as you see them at the bottom.

[Slide]

DMARDs and now biologic DMARDsB-methotrexate without any question is the most commonly used disease-modifying agent that pediatric rheumatologists use. This has a specific indication for polyarticular JRA. The starting dose is as described. There has been one study of methotrexate and leflunomide. This was done in 240 patients. It was a 16-week double-blind, 6-month extension plus an optional 30-month extension in JRA. The primary efficacy endpoint was the JRA definition of improvement greater than 30 percent. The responder results of that were 89 percent with methotrexate compared to 68 percent with leflunomide. The adverse events are as you see them with, again, gastrointestinal being quite prominent.

[Slide]

Sulfasalazine is approved for pediatric use. It is indicated for polyarticular JRA. It has an older childhood cutoff, if you will. This

is indicated for children 6 years of age and older. The adverse events are described at the bottom. Again, gastrointestinal, headache and rash are some of the more frequent adverse events.

[Slide]

When we shift to biologic DMARDs, Enbrel has approval for pediatric patients with JRA. This is a cytokine antagonist. The age group again differs somewhat. This is indicated in JRA patients who are 4 to 7 years of age who have had an inadequate response to one or more DMARDs. The dosage is as you see it, and this is a subcutaneous injection. The adverse events are headache, nausea, abdominal pain. These adverse events are specifically taken from the study that was completed for this indication. The serious adverse events that were reported in that study are as you see them listed here.

[Slide]

DMARDs that are indicated for adult rheumatoid arthritis without an indication for JRA are hydroxychloroquine, injectable gold,

leflunomide and d-penicillamine. These are not used very frequently now in patients with juvenile rheumatoid arthritis.

There are other immunomodulatory or cytotoxic drugs. Those that are indicated in adult RA without a JRA indication are azathioprine and cyclosporine A. Those without an adult RA indication or a JRA indication are chlorambucil and thalidomide.

[Slide]

If we look at the treatment in 2006 for pauciarticular JRA, the overall message is that treatment is more aggressive. Twenty-five to 33 percent of children with pauciarticular JRA will respond to a non-steroidal agent. The children who are not responsive to an NSAID within approximately 4-6 weeks, those children for example who have flexion contractures, leg length discrepancy, etc., most likely will receive intra-articular steroids for those joints that are resistant to the NSAID treatment. Patients with extended pauciarticular JRA or small joint involvement are treated very

much as we would approach a child with polyarticular JRA.

[Slide]

For polyarticular, whether that disease is rheumatoid factor negative or positive, rheumatoid factor positive tends to be the more aggressive form. We first try NSAIDs but they are usually not as effective as a non-steroidal plus a DMARD. A trial of an NSAID may last for just a few weeks. Oral methotrexate would be the most likely medication that would be started next. If the oral methotrexate is not effective a parenteral form of methotrexate would be started. If those two together are not effective an anti-TNF medication would most likely be started. There is no current evidence as to whether a combination of methotrexate plus an anti-TNF medication is more effective than only an anti-TNF medication.

[Slide]

If you look at systemic disease with systemic features, NSAIDs would probably be tried for maybe 2 to 3 weeks with caution. There is a

very high risk in this subset of JRA for disseminated intravascular coagulation, macrophage activation syndrome.

Intravenous pulse methylprednisolone is certainly used in this group children mainly to control their systemic features. Oral corticosteroids are used. Certainly, pediatric rheumatologists try to use the lowest dose possible. Steroid-sparing agents include the immunomodulatory approach. There are many new agents that are under evaluation for additional steroid-sparing effects.

[Slide]

The celecoxib supplement is under review today. It is categorized as a non-selective NSAID/COX-2 selective inhibitor. The proposed formulation is a capsule, a 15 mg capsule, with the option to use this as a sprinkle onto applesauce.

The pivotal study submitted is a 12-week double-blind, plus a 12-week open-label extension study which included 240 patients with JRA. A celecoxib oral investigational suspension was used

and an oral naproxen suspension was the active comparator in the trial.

The proposed dosing in patients with JRA is in two categories, a 50 mg capsule BID, which would be 100 mg total daily dose. This is based on weight. This would be for children between 10-25 kg. The second category based on weight is a 100 mg capsule twice a day, for a 200 mg total daily dose. This is for children greater than 25 kg. Thank you for your attention.

DR. BATHON: Thank you. Are there any questions for Dr. Yancey?

[No response]

Thank you. Moving along, our next presentation is by Dr. Sharon Hertz, Deputy Director of DAARP at CDER, at the FDA.

Cardiovascular Risk and NSAIDs

DR. HERTZ: Good morning.

[Slide]

Now that we have heard about the need for additional therapies to treat this terrible disease, I am going to review some of the safety

concerns with respect to cardiovascular risk.

[Slide]

I am going to review what we currently know about the cardiovascular risk associated with NSAIDs and I am going to focus on the information that we have obtained from celecoxib and rofecoxib. Then I will also discuss some of the conclusions that our agency has made once we reviewed the information.

[Slide]

Rofecoxib was initially approved in 1999. The original NDA had a database of about 5,000 patients, with over 700 exposed for 1 year at the 12.5 mg and 25 mg doses. There was no apparent cardiovascular signal from this original application. There was only a few number of events and there was no dose response for the few events that occurred.

[Slide]

Subsequently we had VIGOR, which was a large outcome study designed to explore the gastrointestinal safety of rofecoxib, and also

looked at cardiovascular outcomes. Eight thousand rheumatoid arthritis patients were enrolled, and this was an active comparator study with naproxen as the comparator. A high dose of rofecoxib was explored in this study. The median exposure was nine months.

[Slide]

This study did reveal a cardiovascular risk, with a relative risk ratio of 2.37 for serious cardiovascular events, and in particular the MIs really stood out with a relative risk of 5. These events were explored in an advisory committee in 2001.

[Slide]

We then had additional studies of rofecoxib compared to placebo in 3 clinical trials that were exploring the ability of rofecoxib to slow progression of Alzheimer's or to prevent onset. These studies looked at the 25 mg dose of rofecoxib and ranged from 15-24 months in duration. Here there was no consistent signal for cardiovascular events.

[Slide]

Then we found out that there was a signal against placebo in a study called APPROVe. This study was evaluating the effects of rofecoxib to reduce the incidence of adenomatous polyps in patients with a history of colorectal adenomas. This was a large placebo-controlled trial intended to study patients over 3 years with an additional year of follow-up. It also explored the 25 mg dose of rofecoxib. Approximately 2,600 patients were enrolled.

[Slide]

In September of 2004 we were informed by the company that there was a cardiovascular signal. For all serious cardiovascular events there was a risk of about 1.8. For MI it was a little higher. Subsequently the product was withdrawn from the market.

[Slide]

Turning to celecoxib, we originally approved celecoxib in 1998 and, again, with a reasonably sized safety database there was no

apparent cardiovascular signal.

[Slide]

CLASS was the large outcome study that explored the GI safety profile for celecoxib. The study enrolled about 8,000 patients with OA and RA and compared celecoxib 400 mg twice daily, a fairly high dose, with ibuprofen or diclofenac and no apparent cardiovascular signal was present during this study versus these active comparators.

[Slide]

The next set of study results that we explored with respect to cardiovascular outcomes came from a study looking to see whether celecoxib could prevent sporadic colorectal adenomas. This was a large double-blind, placebo-controlled study in approximately 1,900 patients looking at two doses of celecoxib compared to placebo.

[Slide]

Later, in 2004, the study was halted because a cardiovascular signal was detected. The relative risk for the lower dose, 200 mg twice a day, was 2.5 compared to 3.4 for the higher dose.

There was another colon polyp prevention study, that was also going on concurrent with APC. This was a 400 mg once daily dose of celecoxib and it didn't have the same type of signal that APC revealed.

[Slide]

Here are some results from APC. You can see that there is fairly good separation here, especially with the higher dose, from placebo for the cardiovascular events.

[Slide]

Another study going on about the same time that was ADAPT. This was an Alzheimer's prevention study. This study was halted in the wake of the information coming from the APC trial. There is no clear cardiovascular risk for celecoxib based on the composite endpoint used for celecoxib compared to placebo while there is a suggestion of a possible risk for naproxen. This is the only placebo-controlled study we have so far for naproxen.

[Slide]

So, following the results from APPROVe and APC, we convened an advisory committee in 2005. Several people here were there. Data was presented for all of the available NSAIDs, those approved in this country and other products not yet approved in this country.

[Slide]

We also explored at that time the epidemiologic studies that were available. One consistent finding across the epidemiologic studies was a consistent risk of cardiovascular events associated with higher doses of rofecoxib, over 25 mg per day. The findings were variable for risk associated with other selective and non-selective NSAIDs. In particular, some studies showed an increased risk of celecoxib but others didn't.

[Slide]

The agency crafted a decisional memo that was released in April of 2005.

[Slide]

The conclusions drawn from a review of all the information prior to and during the advisory

committee were that there is, in fact, a risk for serious cardiovascular adverse events associated with the three approved COX-2 selective NSAIDs, the three that were approved in this country, but that the data did not warrant a rank ordering of the risk across those products.

[Slide]

Additionally, the information available from large long-term controlled studies suggested that there was no greater risk for the COX-2 selective products than the non-selective products.

[Slide]

It was noted that long-term placebo-controlled studies for the non-selective NSAIDs were generally not available and, pending the availability of additional data, it was most prudent to interpret the findings as consistent with a class effect of an increased risk for serious cardiovascular events for COX-2 selective and non-selective NSAIDs. As a result, we asked for labeling changes for the class that included a boxed warning. We also issued a class medication

guide and revised the warnings for the over-the-counter NSAIDs.

[Slide]

Additionally, we tried to see if there was other information that could help us understand the risk for other approved NSAIDs, and we asked companies to look at the controlled trial data that they had on record for all the approved NSAIDs. When we reviewed the information that came in what we found was that we couldn't draw any additional conclusions about cardiovascular risk. The studies were small. Even with pooling, the number of events was too small to support any conclusions and most of the studies were just too short in duration.

If there are any questions, I can entertain them.

DR. BATHON: Dr. Gorman?

DR. GORMAN: Dr. Hertz or Dr. Yancey, is there any plausible biological reason to believe that children with JRA are at greater risks for cardiovascular events with these diseases?

DR. HERTZ: Well, I can start the answer and then I will defer to the rheumatologists. I think the question here is not just whether the children, during their initial year or few years of therapy, are at increased risk per se but, given that we believe that these drug products carry a risk, what are the implications for treating this population for an extended period of time?

DR. GORMAN: I understand that risk. In children with JRA is there a plausible biological explanation for the committee to consider whether they are at increased risk for cardiovascular events in general?

DR. HERTZ: I would defer that to someone else.

DR. GORMAN: Maybe a different way to ask the same question is as children with JRA reach adulthood do they have a normal life expectancy, and is the distribution of cause of death different than the general population?

DR. LEHMAN: I think if you look through the literature, you will find that while there is

very clear data in the adult rheumatology population coming out of Ted Pincus' long-term studies, the pediatric data doesn't really exist in a good form. You need to keep track of children for 30, 40 or 50 years to start accumulating that data, and when you start trying to get data on long-term follow-up of children grown up to be adults you have significant bias of ascertainment because children who got well and have no further problems are clearly lost to follow-up, gone to school, moved to other locations. They are very difficult to follow.

At the same time, you have to consider that all inflammatory conditions appear to be associated with a greater risk of cardiovascular disease and this is another inflammatory condition. In that, you are going to have to balance off the risk/benefits of treating and decreasing the inflammation versus the fact that all these inflammatory diseases do appear to carry an increased risk. But clear, objective long-term data for pediatric patients doesn't exist.

DR. GORMAN: Thank you.

DR. BATHON: Dr. Davis?

DR. DAVIS: John Davis, San Francisco. I was wondering if you could comment a little bit furtherB-I think you went over this a bit quickly--on the time needed to detect the cardiovascular signal in the studies. You said that initially the FDA approved these drugs based on the limited data that you had but as studies went on and you had longer follow-up there was a cardiovascular signal. So, could you specifically comment on how long it took on average to detect that signal?

DR. HERTZ: Sure. I don't think it was so much the duration of the studies because we did have year-long data. If you look at rofecoxib for instance initially with VIGOR, it was a larger study with the longer duration and a higher dose, which I think is possibly one reason why we saw it in an active-controlled study.

For celecoxib, again, even with CLASS which was a larger study we didn't find the signal.

What perhaps permitted the signal to be detected was the placebo comparator in a large study over a period of time.

It is challenging because based on our conclusions and our review of the data we think that there is a class effect. So, many of these studies are active-controlled and it was the opportunity to explore the NSAIDs in non-traditional settings, for instance, in placebo-controlled trials for polyp prevention, or we also explored some of that with the Alzheimer's disease studies, and I think it was the ability to distinguish from placebo that was very helpful in detecting a signal compared to some of the other studies. In the arthritis conditions and some of the other indications it is hard to do year-long placebo-controlled studies. You just can't maintain a population that long. So, in the active-control studies I think we lost some of that sensitivity because there may very well be a cardiovascular effect for the comparator as well.

DR. SANDBORG: Christy Sandborg, Stanford.

Is there any understanding of the pathogenesis of this effect?

DR. HERTZ: There are theories, and I don't know that I can get into them in great detail right now, but initially what was considered was that the relative COX-2 selectivity may contribute to the ultimate thrombotic events. It is not entirely clear if that is really the cause or not, particularly since when we look at some of the active-controlled trials that don't distinguish the COX-2 selective from the non-selective NSAIDs we don't differentiate it because the non-selectives have a lot of COX-2 selectivity themselves or activity themselves. I mean, we just don't know. Some have thought that it might be a blood pressure effect. I think that right now we don't honestly know what the actual mechanism directly is.

DR. BATHON: Dr. Proschan, do you have a question?

DR. PROSCHAN: Yes, I was just wondering whether there is any data after these trials. You know, once they stopped did the curves seem to come

back together or did they continue to be separated?

DR. HERTZ: Well, we have longer-term follow-up data in the APPROVe study because one of the questions from the original study was once you went off NSAID therapy what happened to your colon polyps. So, we do have a year off therapy there and we have been reviewing the study results internally.

I think that there have been several comments publicly about the risk after discontinuation and it appears that the risk may resolve over time. But I don't know that we have definitive answers. But based on what we do have from APPROVe, it does look like it may decrease over time. Part of the problem there, again, is that we start losing numbers so it becomes very hard to know for sure.

DR. MORRIS: Can you bring up slide 13, the APC study?

[Slide]

In that slide it says p is equal to 0.01. But my question is at what point does a difference

emerge over time?

DR. HERTZ: This varies quite a bit by study. We start to see really something at the 12-month point, here. I don't think I have with me any really good specific analyses looking at time. It depends. It depends on what composite outcome you look at. We generally see the data presented in a couple of different formats. One is a composite that is called the APTC trialist outcome. It is from a collaborative for the antiplatelet trials, where we combine fatal and non-fatal MI and stroke and it also includes hemorrhagic strokes and cardiovascular death. In some of the large studies that endpoint may start to separate earlier and we may see separation in some of the studies before a year. Using all serious cardiovascular thromboembolic events, which is a bigger set, some of the time we see separation later and it may be because some of the events included in that definition may have a different mechanism, may not be thromboembolic.

DR. BATHON: Dr. Proschan, did you have a

comment?

DR. PROSCHAN: Yes. I think it is really hard to tell from this picture because, I mean, there are only seven events in the placebo group.

DR. HERTZ: Right. I thought I could get away with a brief overview and I guess maybe a little more detail would have been better. But, depending on which curves you look at, which graphs and which studies, the results do differ. But we do see some separating before a year and we see some separating later.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: Getting back to the question of pathogenesis, which is something I don't understand, were there any signals in the animal studies at very high doses of cardiovascular effects of this drug in particular or any of the NSAIDs?

DR. HERTZ: I have my pharm. tox. folks there and they are shaking their heads no, and we didn't have a good signal of any sort from the non-clinical work. There was a theoretical

concern, which is why the cardiovascular outcomes were included in the large GI studies. It was really thought that COX-2 selectivity could be a mechanism that would promote thrombotic events and, therefore, it was pre-specified in these clinical trials so that we could try and get information. But, because we see some of the non-selective NSAIDs not distinguishing in terms of event rates from the selective, it is hard to really feel comforted that it is a COX-2 selective drug event. Do you want to add to that? So, is it just any inhibition of COX-2 rather than a selective inhibition of COX-2? I mean, we just don't have the answers right now. Yes, there is a lot of work in animal models now using different rodent models. Garret Fitzgerald, for instance, is doing a lot of work here. And, I don't think we really have one good, consistent theory that overrides the others.

DR. BATHON: Dr. Boulware?

DR. BOULWARE: Dennis Boulware, from UAB. I am sorry to distract you. I was trying to get the Chair's attention--

DR. HERTZ: I was hoping you were going to help with the answer!

DR. BOULWARE: No. Actually, at the risk of adding more complexity to this issue, can you comment again on the effect of low-dose aspirin in terms of the observed outcomes of the MIs and, if there is one, could a pediatric rheumatologist tell us how commonly low-dose aspirin is used in pediatric populations in treating this condition?

DR. HERTZ: I thought that question might come up. We did go back and look at the effects of aspirin at the time of the original presentation of data. VIGOR didn't permit the use of aspirin. Anyone who required aspirin for cardiovascular prophylaxis was excluded from the study. But aspirin was allowed in APPROVe, CLASS and in studies with a couple of the unapproved products. And, the best that we can say right now is that it has been an inconsistent effect. So, sometimes it seems to mitigate the risk but other times it doesn't.

I don't have the data exactly presentable

so I won't start talking numbers, but it hasn't been a consistent protective effect. So, all we can say for sure is that we know the aspirin worsens the GI risk and it is not clear that the value for cardiovascular protection can balance that. We don't have that strength of evidence.

DR. BATHON: Would any of our pediatric rheumatologists like to comment on the question about aspirin? Dr. Sandborg?

DR. SANDBORG: Typically in JRA we don't use low-dose aspirin because the risk is extremely low of cardiovascular. We do use it for other diseases such as pediatric lupus, and such, so it is not a typical thing. But I was struckB-I can't remember the name of it, it is not the APC adenoma study but the other one where, clearly, the use of low-dose aspirin did not distinguish between the groups.

DR. HERTZ: In APPROVe.

DR. SANDBORG: In APPROVe.

DR. BATHON: Dr. Daum, you had a question?

DR. DAUM: Yes. I would like to ask

whether, armed with the clarity of the retrospectroscope, always a powerful tool, can you comment on data submitted to the FDA from studies that did not show an increased incidence of cardiovascular events?

DR. HERTZ: Yes, we went back and looked at that quite carefully last year, specifically looking to see what we could learn. You know, is there some way to approach this now that we know that there may be a signal? That is when we went back and looked at the original NDA data where we looked at some of the other studies like the Alzheimer's studies that didn't have an apparent risk, and it just doesn't seem to be there. You know, if there is an excess of one or two events, even now that we know that there is a risk it is hard to really say aha! So, no, even looking back it is not apparent that there were any actual signals in those other studies.

DR. DAUM: And how did the agency interpret that retrospective look?

DR. HERTZ: You don't see all findings in

all studies. In the Alzheimer's studies that had placebo controls that didn't show risk maybe there was something different about the patient population than the younger polyp study populations. We don't have study results in the same population under similar conditions with multiple treatment variables so that we can get a really firm idea. We have these cross-study comparisons and there are just so many variables that it is hard to know which was the variable responsible that allowed a signal to come through in one condition but not another.

DR. BATHON: Dr. Weise?

DR. WEISE: A two-part question. JRA is a condition with flares and remissions. I wonder if someone could speak to the pattern of use of NSAIDs in standard JRA treatment? For instance, is it short term? Is it long term to avoid further flares?

The question that follows on that is do we have any data that shows whether on-again, off-again use of NSAIDs, as opposed to long-term

use, changes the risk of cardiovascular events?

DR. BATHON: Dr. O'Neil, can you address that?

DR. O'NEIL: I will try to stick to the common usage of NSAIDs in pediatric rheumatic diseases, particularly JRA. This is a subject, as Dr. Yancey presented, where the trends are under constant revision based on the availability of increasingly effective medications. For example, the biologic agents have changed the use of NSAIDs and the role of NSAIDs in management of children with JRA. They are still used as they are the only anti-inflammatory drug that we have to control the disease that is a pain reliever at the same time.

So, that is one unique niche for this class of drugs. So, most people will use it if the child is having symptomatic pain. It is used as the initial treatment because of its relatively benign profile of toxicity in children and its longer track record. It is often used as an initial treatment to see if the child will respond to that drug. In most cases it is used long term,

or at least weeks to months, and then as the inflammation comes under control, I think increasingly the trend in pediatric rheumatology is to back off from this class of drugs and use the more potent anti-inflammatory agents as control of the initial disease has settled down. It is then, again, not uncommon to use an NSAID in a flare to help somebody get over the edge and settle down the disease when they have a flare.

DR. BATHON: Would you say that there has been a trend towards less continuous use and more intermittent use over time?

DR. O'NEIL: There has been, but I think to say intermittent useB-I don't think most of us use it as a medication until the disease has been under pretty good control and then we keep it under good control, or we think it is good control. Again, as you know, there are questions there as to what really is good control but for weeks or months before we back off though.

DR. BATHON: Dr. Lehman?

DR. LEHMAN: I think it is important in

terms of the way we are viewing this to understand that while there is some intermittent use of non-steroidal anti-inflammatories these are basically long-term drugs for kids with active disease. We need to separate out the different subtypes. Pauciarticulars may very well resolve over a relatively brief period and be off medication and not need medication for years. But polyarticular children or children with systemic onset disease that persists are going to be on these drugs for six months to several years at a time. There is no weeks of treatment or days of treatment in general.

DR. BATHON: Any other questions or comments?

DR. YANCEY: Just to answer the second part of your question, we have not seen cardiovascular long-term studies in children with JRA.

DR. DAVIS: And what percentage of pediatric patients will go on into adulthood with the chronic forms?

DR. HERTZ: I will defer that to the

pediatric rheumatologists.

DR. BATHON: Could one of the pediatric folks answer that?

DR. YANCEY: We see the most difficult long-term outcomes in polyarticular JRA rheumatoid factor positive. We also see very difficult articular outcomes in aggressive systemic disease. Rarely will pauciarticular evolve to a polyarticular course or behave as a polyarticular and we would approach them treatment-wise as we would a child with more aggressive polyarticular disease. So, percentage-wise, polyarticular, 40-50 percent. For systemic disease it can be as high as 60 percent.

DR. BATHON: Any other questions or comments?

DR. TURK: I have a question about the response to the NSAIDs. It is my understanding...[inaudible].

DR. BATHON: Dr. Turk, I am afraid we can't really understand you.

DR. TURK: Let me try again. I am trying

to understand the intermittent versus the constant use of the drug. I understand that there are three different subtypes that we are referring to. Is it likely that the NSAIDs are going to be used for months and years on an intermittent basis, or is it that there are...[inaudible]. Just clarify the use of chronic versus episodic.

DR. BATHON: Dr. Lehman?

DR. LEHMAN: It will generally be used for months or years. Although there are certainly circumstances where they will be used more briefly, the vast majority of the time we are using these drugs for months and in the more severe cases often years. I think less frequent dosing is uncommon.

DR. TURK: Thank you.

DR. BATHON: Dr. Sandborg, do you have a comment?

DR. SANDBORG: No, I think one of the key things is really looking at different subtypes so for oligoarticular a typical course might be anywhere from six months to two years because these children often go into remission and this remission

can be for years sometimes. So, over their course, up to age 18, they may have up to three or four major flares for which they would require NSAIDs and then be off of it in between. Then there is 50 percent of children with the polyarticular or systemic over a very long-term chronic course that may be on NSAIDs for the majority of their childhood, and those are the children who often go on into adulthood with active disease.

I think one of the moving targets here in rheumatology, both in adults and pediatrics, is that with improved medications we are actually at a point where we are not as dependent on using long-term NSAIDs as we once were and we are actually able to, in many cases, use them more intermittently but this is too early to know the scope, magnitude or exactly what the time frames are of this usage.

DR. BATHON: Dr. O'Neil?

DR. O'NEIL: This is Kathleen O'Neil and I just wanted to further clarify my comments. As Christy pointed out, we are in the process of

changing the way we treat these patients but still the majority of them do get long-term non-steroidal anti-inflammatory therapy, particularly the 50 percent that have oligoarticular disease and are managed largely with non-steroidal anti-inflammatories, again, the typical course being maybe two to three years of their childhood, perhaps longer, some of them much longer, ten years or so. The children with polyarticular disease are much more likely to wind up on a biologic agent and other disease-modifying agents. Then, at that point in time, usually at least six months if not a year or more into their course, they may be able to come off NSAIDs as a daily drug but still may need it with flares. So, it is an evolving landscape but we are still talking about long-term use.

DR. BATHON: So, it sounds like we are saying that kids with polyarticular disease who have chronic disease are more likely to be on chronic NSAIDs, although there might be a trend towards a little bit less stringency with advancing biological and DMARD therapies. The kids with

oligoarticular disease are more likely to have intermittent use, but still months to years at a shot, so still fairly chronic use. Are there any other questions or comments? Yes, Dr. Morris?

DR. MORRIS: While we are on this topic, do we know what percentage of children are treated by specialists versus generalists, and to what extent are these pediatricians or experts in arthritis and rheumatology? Do we have any idea?

DR. BATHON: Anybody want to answer that? Dr. Sandborg?

DR. SANDBORG: Actually, this has been an area of interest and study, and because of the scarcity of pediatric rheumatologists it looks like probably, depending on geography, pediatric rheumatologists care for perhaps somewhere between a third and half of the children with rheumatic diseases. In some areas where there are few pediatric rheumatologists it is much less.

DR. CHESNEY: I am intrigued by Dr. O'Neil's comment that the NSAIDs are required for pain. I take it that means that the other

therapies don't manage the pain. Are there other analgesics that have been used over the years? Has anybody looked at the issue of using the NSAIDs intermittently with all of the other non-NSAID use, in other words, stopping them to see if the pain recurs?

DR. O'NEIL: The short answer is that there have not been formal studies to address your question. The long answer is that, yes, there is intense interest in pain control research in juvenile arthritis and a number of different agents are used, including narcotics occasionally. A variety of agents are used. But I think for ease of use and cost non-steroidals tend to be used primarily.

Also, we try to practice evidence-based medicine and the evidence is always old. By that, I mean that non-steroidal anti-inflammatory medications and corticosteroids are the drugs that are old enough to have a track record of use in childhood and when you treat these children you are obligated to try to use what has been proved before

you venture where there is no track record.

DR. BATHON: Dr. Gorman?

DR. GORMAN: Could any of the pediatric rheumatologists talk about the present frequency, in 2006, of cardiovascular events in the juvenile rheumatoid population? Common? Uncommon? Rare? Unheard of?

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: Well, I can throw in that that is basically unheard of or very rare in children with JRA.

DR. BATHON: Dr. Yancey?

DR. YANCEY: Just to expand on what Dr. Sandborg said, rare, but I would direct your attention to the children with systemic JRA who clearly have pericarditis, cardiac tamponade, myopericarditis, hypertension. So, just keep that in mind.

DR. BATHON: Dr. Lehman?

DR. LEHMAN: I think one of the things that we need to pay attention to in asking that question is looking back at conditions where we know there

is an increased risk in childhood. But if you look at lupus or other diseases where they are treated with a large amount of corticosteroids where the risk is obvious and well-known, the cardiovascular events are not occurring until they are in their early 20s and early 30s. So, it is quite true that if you survey pediatric rheumatologists during the pediatric age the incidence of cardiovascular disease is virtually zero. But whether that is meaningful in terms of follow-up when they get to their 20s and 30s, that is where we are seeing it with the drugs that we do know cause a problem. So, expecting that we would be seeing it in the pediatric age group for these drugs is probably inappropriate. We really do need to look at these people in their 20s and in their 30s.

DR. BATHON: It is also useful to remember that some of the studies in adults are now looking at subclinical markers of cardiovascular disease rather than just depending on events. You could argue about the accuracy of these subclinical measures as surrogates for cardiovascular events

but there have been relatively few, as I understand it, subclinical studies of cardiovascular disease in kids. There are a couple suggesting that there might be an increased prevalence of subclinical early atherosclerosis but they are relatively rare. Dr. Sandborg?

DR. SANDBORG: To clarify that, certainlyB-and perhaps the infectious disease folks can help with thisB-in patients who have Kawasaki's in early adulthood there are these subclinical findings of atherosclerosis in those patients where that is an actual vasculitis of the coronary arteries, direct vessel inflammation. Certainly, in young women with lupus getting into their 30s and 40s the risk of subclinical atherosclerosis is very increased. In children there are no good studies in pediatric lupus of the cardiovascular risk, although there are some studies ongoing now that will, hopefully, illuminate this.

DR. BATHON: We are going to take one last comment or question. Mr. Levin?

MR. LEVIN: Just back to Dr. Morris'

question, is it appropriate to ask if the sponsor has that data on the breakdown between children with JRA under the care of specialists and under the care of generalists?

DR. BATHON: I think we will postpone that until we hear from the sponsor. On that note, we will move on to the sponsor's presentation, and this is by Pfizer. We will first hear an overview by Dr. Lowery, followed by a presentation on treatment of JRA by Dr. Dan Lovell, from Cincinnati, and then we will hear from Dr. Lowery again.

MS. CLIFFORD: We are going to take just a few minutes and just reload, just a few minutes. Thanks.

DR. BATHON: Why don't we take this opportunity to take a 10-minute break? We will meet back here at 9:30 sharp.

[Brief recess]

MS. CLIFFORD: If you are intending to speak in the open public session and have not registered with our desk right outside, in the

lobby, could you please take a moment and do so? Thank you.

DR. BATHON: I would like to get started again. When we do have another session of questions I am going to ask each of the committee members to please identify yourself before asking your question so that the audience and people who listen to the tapes, and so forth, can know who you are. Thank you.

Sponsor Presentation

Celecoxib in the Treatment of Juvenile Rheumatoid Arthritis

DR. LOWERY: Good morning.

[Slide]

My name is Dr. Simon Lowery. I am the medical and development lead for celecoxib at Pfizer. I would like to thank the committee, the agency and guests this morning for the opportunity for me to speak on the subject of celecoxib in the treatment of JRA.

As mentioned by one of the earlier speakers, I will just take a moment to mention that

because our study of celecoxib in this condition predated changes in the terminology of juvenile arthritis we will refer to this condition as JRA.

[Slide]

With us today are a delegation of experts in their fields who have assisted us with our study of this condition with celecoxib, and at times I may call upon them to provide their insight and advice.

[Slide]

Our objectives this morning are four-fold, first of all, to highlight the medical need for NSAIDs in the treatment of this disease; to present for committee discussion the available data for celecoxib in the treatment of children with JRA; to demonstrate that, based on the available data, celecoxib has demonstrated efficacy and there is no current evidence for unique safety concern compared to other NSAIDs. We will, however, highlight a concern for rare events and uncertain long-term risks shared by all NSAIDs.

[Slide]

I will do this in the following manner by giving a brief overview. Dr. Hertz has covered some of my points so I will cover them briefly. I will then hand over to Dr. Lovell, a practicing pediatric rheumatologist, to give his own specific personal insights into the treatment of this disease. I will cover the available data for celecoxib in this condition and then conclude.

[Slide]

Celecoxib is a selective inhibitor of the enzyme COX-2 and spares COX-1 enzyme at therapeutic doses. It was approved in 1998 for the adult indications of OA and RA, and subsequently, in 1999, as an adjunct for usual care and for adenomatous polyposis coli. In 2001, for acute pain and primary dysmenorrhea and most recently, in 2005, for ankylosing spondylitis. In total, celecoxib has been studied in over 25,000 adult patients. We have epidemiologic data for celecoxib in around 200,000 patients and total experience in the marketplace in over 70 million patients since approval.

[Slide]

As referred to earlier, in September of 2004 rofecoxib was voluntarily withdrawn from the market by its manufacturer due to increased cardiovascular risk. Shortly later, we observed in one long-term placebo-controlled trial a dose-related increase in cardiovascular risk with high doses of celecoxib compared to placebo.

[Slide]

Shortly afterwards the agency convened this committee to discuss the benefits and risks of both selective and non-selective NSAIDs. Overall, the committee voted 31-1 in favor of continued marketing of celecoxib. Shortly afterwards the FDA issued a memo, as discussed briefly earlier, questioning cardiovascular risks with all NSAIDs and requesting changes be made for all labels for all prescription NSAIDs. Subsequently class labeling was implemented for cardiovascular and gastrointestinal risk.

[Slide]

The FDA memorandum stated, "it is not

possible to conclude at this point that the COX-2 selective drugs confer an increased risk over non-selective NSAIDs in chronic use."

"We believe that it is reasonable to conclude that there is a 'class effect' for increased cardiovascular risk for all NSAIDs pending the availability of data from long-term controlled clinical trials that more clearly delineate the true relationships."

[Slide]

A boxed warning was put into place for all NSAIDs, whether they be selective or non-selective, stating that the drug in question may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke which may be fatal; that all NSAIDs have similar risk. This risk may increase with duration of use, and patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

In addition, the agents are contraindicated for use in the perioperative

setting of coronary artery bypass surgery and, in addition, further GI risk labeling warnings were added.

[Slide]

Subsequent to these findings, recent data have solidified this position that all non-steroidal agents, whether they be selective or non-selective, may be associated with cardiovascular risks. These data are the final published data from the ADAPT study mentioned earlier. ADAPT was an Alzheimer's prevention study in an elderly population, looking at whether celecoxib or naproxen would prevent the onset of Alzheimer's disease. Celecoxib was dosed at a high dose, 200 mg BID, for several years of therapy; naproxen, lower than its full therapeutic dose in arthritis, at 220 mg BID.

Looking at endpoints from the APTC collaboration endpoint of MI, stroke and cardiovascular death through to the APTC endpoint in addition to congestive heart failure and TIA, naproxen demonstrated significantly increased

cardiovascular risk for the endpoint of APTC plus CHF and TIA but not for the other two endpoints. Celecoxib did not demonstrate significantly increased risk for any of the three endpoints.

[Slide]

In addition, recent data from researchers in Australia performed a meta-analysis of available observational data in approximately 5,000 patients in total. These data demonstrated significantly increased cardiovascular risk with a number of other non-selective NSAIDs such as diclofenac, indomethacin and meloxicam. Thus, in recent times more data has become available increasingly solidifying the conclusions made in 2005 that both the non-selective and the selective NSAIDs may have a degree of cardiovascular risk, and this risk may be associated with duration of therapy.

[Slide]

On our part, Pfizer is committed to more clearly delineating the exact risk for cardiovascular serious events with celecoxib compared to two commonly used NSAIDs, naproxen and

ibuprofen. The PRECISION trial, Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen, has recently started enrolling patients. This study will take several years to complete, though we hope it will finally answer the question of whether selective inhibition of COX-2 is truly, or not, more dangerous from a cardiovascular standpoint compared to non-selective inhibition. The study will exclude an upper bound of a 95 percent confidence interval of 1.33 and a point estimate of 12 percent compared to these two treatments.

So, that concludes my brief introduction. I would now like to hand over to Dr. Dan Lovell to give his personal insight into the condition of JRA. Then I will return to cover the available data for celecoxib in this condition.

Juvenile Rheumatoid Arthritis: Clinical Overview

DR. LOVELL: Thank you.

[Slide]

It is an opportunity that I am honored to have to speak to the Arthritis Advisory Committee.

I have been asked to speak as a practicing pediatric rheumatologist, which I have been for 25 years. I hope that in the brief time we have together I can portray for you the picture of JRA that I see when I treat kids every day, which is a disease that can, and oftentimes does, negatively impact many aspects of the children's lives, and many patients persist into adolescence and young adulthood.

[Slide]

My task was made very much easier by the excellent presentation by Dr. Yancey and the comments from my pediatric rheumatology colleagues on the board so I don't need to go through most of this slide but I do want to make a few points. That is, for the children who have pauciarticular course JRA NSAIDs are oftentimes the cornerstone of their therapy and many of these children are adequately treated with the NSAID therapy alone or NSAID therapy with intermittent intra-articular steroid injections. The duration of that therapy can be a matter, as others have said on the board,

of months to years.

Polyarticular course patients have more severe disease. NSAIDs are still very commonly used, and used for longer periods of time but they are used in association with other agents such as DMARDs, primarily methotrexate, and increasingly biologic therapy.

For the systemic JRA patients an even larger number of therapeutic agents are used but, again, non-steroidal anti-inflammatories continue to be part of their treatment profile.

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Pain is a common and persistent manifestation of this disease. This is a study that was done in our center, where we have been asking children to report their JRA-related pain for over 20 years on a regular basis. This is a study in over 400 kids with JRA who were followed for at least 5 years. What you see is that at their first visit over 60 percent of the kids report JRA-related pain. When you look at them 1 and 5 years later, despite intensive therapy, pain

persists in a lot of these patients.

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Moreover, this pain impacts many aspects of the children's lives. So, in this study they asked the parents to assess how often the JRABrelated pain impacted the other aspects of the child's life. What you see here is that 65 percent of the kids have JRA-related pain that negatively impacts their ability to participate in sports and, as we all know, participation in sports is a very important way for kids to be a participant in their peer group. But it is also severe enough to impact their appetite and in 45 percent of the kids it negatively impacts their quality of sleep, their ability to perform their favorite activities, and it impedes their ability to do school work and it also impedes their ability to relate to their friends.

So, this pain is something that gets across many aspects of these children's lives. The subtype JRA patients that were included in the study are shown here, and they are similar to the

kinds of patients we have seen in our clinical trials.

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But JRA can do a whole lot more than just cause pain. This is a study of presence of erosions, irreversible joint damage in kids with JRA as assessed by plain x-ray after 5 years of disease duration. What you can see is that almost 30 percent of the kids with systemic onset, 15 percent of the kids who have persistent pauciarticular course, which is what we consider the less severe form of the arthritis, and almost 70 percent of those with polyarticular course JRA have evidence of irreversible joint damage on plain x-rays. If you were to visualize these kids with more sensitive measurers, such as CT or MRI, you would see that a much higher percentage of the patients in each of these subgroups have evidence of joint damage in the cartilage.

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To look at the outcome of JRA we used a recent meta-analysis that was published in 2005.

It included 21 studies that have been published over a ten-year period and it included kids who had all the various diagnostic or classification criteria for chronic arthritis in children known to man, JIA, JCA, JRA. So, it was very inclusive in its approach. In most of the studies the follow-up was greater than ten years. All told, it combined over 5,000 kids with JRA.

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This slide shows the result of the study. If you look at remission what you see is that for children with pauciarticular JRA the percent of patients that go into remission varies between 40-80 percent. Another way of looking at it is that the disease is persistent in 20-60 percent of the kids. If you look at similar numbers for polyarticular and systemic, you can see that for each of the disease subtypes there is a portion of patients in which the disease persists.

This is functional outcome for the patients. Steinbrocker class III functional outcome means that you have enough impairment by

your disease that you are able to do very few of your self-care activities. Class IV means that you are either bound to a wheelchair or to a bed. I think that all of us would agree that either one of those functional classes are fully unacceptable for a kid. What you see in these studies is that anywhere from 1-27 percent of the patients end up in one of these two very unsatisfactory functional outcomes.

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To get at the question raised by one of the board members about thrombotic risk in kids with JRA, around the time of the voluntary withdrawal of Vioxx we, as a pediatric rheumatology community, had the same concerns the adult rheumatology community had: what is the thrombotic risk for our patients? So, we turned to the Childhood Arthritis and Rheumatology Research Alliance, which is a group that almost all of us in pediatric rheumatology in North America belong to. The voluntary organization focused on better understanding the diseases and their treatment.

Ninety-eight percent of the pediatric rheumatologists in North America voluntarily have joined CARRA.

So, we decided that we would perform a survey amongst the CARRA members so we distributed this survey to 130 pediatric rheumatologists. The question really is in patients with JRA, have you seen any patients who have had stroke, pulmonary embolus, myocardial infarction of DVT? And, was that patient treated with an NSAID or a traditional non-selective NSAID or a more selective COX-2 agent? We also asked the respondents how many years they have been a practicing pediatric rheumatologist.

So, 73 percent of those that received the survey responded. If you have ever done surveys of physicians, that is a very high percent response rate. In that group that responded, it represented over 1,500 years of pediatric rheumatology practice so there was a bunch of people who are at least as old as I am that responded who had been seeing kids for a long time.

The take-home lesson was that in this group of responders there was zero vascular events observed in kids with JRA. There was one patient who had a pulmonary embolism. This was an adolescent who had potential or possible psoriatic arthritis but her use of an NSAID was not for the arthritis but for calf pain that was associated with venous problems that eventually ended up needing up a fasciotomy. So, in the patients with JRA we saw zero vascular events.

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This is a summary of the trials that have been done in kids with JRA with NSAIDs. We rated the trials as those that were performed before 1998 and after 1998, with '98 being the year that celecoxib was approved for use in adults. What you can see is that all these trials were either single-arm active agent trials or active comparator trials, with aspirin being the active comparator. You can see that the sample size here ranged from 18-107 and the blinded intervention phase lasted anywhere from 8-12 weeks, with various periods of

open-label follow-up.

So, based on these trials, tolmetin, naproxen and ibuprofen were approved for the use in children with JRA. You can see that we never had the luxury of having large clinical trials upon which we can base our decisions about children.

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Here are the three trials that have been performed since 1998 in children with JRA. Again, they are all active comparator trials, except that this time the active comparator is naproxen. That is because, as Dr. Yancey said, naproxen has become the initial and first drug of choice for treatment for JRA among the NSAID group.

You can see, again, that these trials are relatively small compared to RA trials, but much larger than the earlier trials and the blinded phase in all these trials lasted 12 weeks, with varying duration of open-label trials. Based on these trials, FDA approved rofecoxib and meloxicam for children with JRA.

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Now, a common characteristic for those three trials I just showed you, those later trials, is that they all used the ACR Pediatric 30 definition of improvement as the primary outcome measure. This core set measures and the ACR Pediatric 30 definition of response is a scandalized, validated, widely accepted outcome measure for trials with JRA. It was initially validated in a data-driven international consensus conference and, since then, it has been prospectively validated in a number of observational and clinical trials.

The core set measures that go into making up the definition of improvement are shown here. They were chosen by this international consensus group to provide a comprehensive review of the way in which JRA can impact people. So, there is a physician assessment of disease activity; a patient or a parent assessment of overall disease impact or overall well being. You can use any of the standardized assessments for ability of the child to perform daily routine functional activities.

Then, we have two measures that reflect the activity of the arthritis, the number of joints with active arthritis and the number of joints with limitation of motion; then the laboratory measure of inflammation which in the trials has been either the sed. rate or the CRP.

To say a person is improved in this ACR Pediatric 30 requires that any 3 of these 6 parameters improve by at least 30 percent and no more than one of them gets worse by 30 percent. In the data we had from prior trials this definition had excellent ability to discern between those patients who responded to methotrexate and those patients who were treated with placebo. So, this has a very robust validation set behind it but it was designed to be used in trials of patients with active polyarticular disease, second-line agent trials.

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What we saw when it was applied to these NSAID trials, in which patients had milder disease, was actually quite surprising I think to a number

of us. What you see here is that in the meloxicam versus naproxen trial this is the percent improvement from baseline in each of these 6 core set parameters for the low dose meloxicam, higher dose meloxicam and for naproxen. What you see is that the mean percent change from baseline actually is a very strikingly large number.

So, I think the take-home lesson is here is that NSAID therapy is not just an analgesic for kids who have an inflammatory disease such as JRA. It improves a number of joints. It improves their ability to do daily functional tasks, as measured by the Childhood Health Assessment Questionnaire. It gets at global disease activity and overall well being. What you see here is that it doesn't have much effect on the sed. rate but in these NSAID trials the vast majority of these children had a normal sed. rate at baseline so that percent change within the normal range isn't terribly informative.

It also has a significant impact on the child's pain. I don't know if you can see it from over there but what we saw in that trial was

anywhere from 44-50 percent decrease in the mean level of pain in these children at the end of 12 weeks.

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Here is the definition of improvement as you apply it in that trial. What you see is that at both time points, after 3 months of therapy and 12 months of therapy, in all 3 dose groups 60 percent or more of these children met the ACR Pediatric 30 level of response. This is the same endpoint we are going to demonstrate later in the celecoxib study. In the celecoxib study we are also going to talk about an ACR 50 and ACR 70 level response, which means that there is a 50 percent improvement in at least 3 of those 6 core set parameters, and the ACR 70, again, is a 70 percent improvement in at least 3 of those 6 core set parameters.

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Here is a summary from naproxen across the NSAID trials in which naproxen was used as an active comparator. What you can see here is that

the proportion of patients demonstrating an ACRP 30 level of response is fairly consistent across these four studies. This is the result from the celecoxib study.

So, what we can see here is that naproxen not only is the first drug of choice, but that it serves as a reasonable and fair comparator drug to use in these active comparator trials at the dose range that has been used in the clinical trials.

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Now let's talk a little bit about the tolerance to NSAIDs in kids with JRA. This is the largest study that we could find that looked intensely at NSAID effect and safety in pediatric rheumatology. So, there were 570 patients with a variety of pediatric rheumatic diseases seen in this clinic. They did a chart review over a 3-year period.

What they found in that population is that if you were taking NSAIDs, then 28 percent of the time you reported abdominal pain. If you weren't taking NSAIDs, it was about 15 percent of the time.

So, it is not clearly NSAID or not NSAID-related in children with rheumatic diseases about the abdominal pain. But if you had abdominal pain and you were taking NSAIDs, then you were evaluated by the gastroenterologist. What they found was that 34 percent of the time you had some evidence of gastrointestinal or gastroduodenal injury. If you weren't taking NSAIDs and had abdominal pain and were evaluated by the gastroenterologist, it was only 7 percent. It is in this group of children with JRA I think that Celebrex may have a particular and special role to play in their treatment because common side effects with NSAIDs are related to the gastrointestinal track.

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This is one of the few studies to look at intolerance to NSAIDs and look at the frequency and the pattern of intolerance. What they showed in this group of 101 JRA patients, all of whom had taken more than one NSAID, is that in this group 78 percent of the patients had to discontinue at least one NSAID due to side effects. If you had to

discontinue one NSAID, then when you got tried on the next NSAID over half of the time you had toxicity with that NSAID and a lot of the time, about 60 percent of the time, it was the same side effect. So, if it was gastrointestinal pain that caused you to discontinue the first NSAID, it is the same story with the second NSAID very commonly.

But what the result of this study was that patients with JRA frequently have problems tolerating NSAIDs. In fact, in the 101 patients in this chart review there were over 400 clinical encounters with NSAIDs that had been tried in these patients so that each JRA patient would have had to try numerous NSAIDs.

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In conclusion, JRA is a disease which is very heterogeneous. It varies from child to child. They have as a common manifestation chronic inflammation, and this chronic inflammation can impact many aspects of their lives in a negative way. Its duration lasts, I think at the shortest, a matter of a few months but in many it is a

long-term disease. The treatment is focused on suppressing that inflammation in a quick and consistent fashion, and NSAIDs have demonstrated in clinical trials the ability to be effective anti-inflammatory agents in patients with JRA.

In general, these NSAIDs are well tolerated, although there are frequent adverse events reported, most commonly in the GI track. Fortunately, the frequency of clinically severe GI hemorrhage or other clinically significant GI-related problems is very minor. In my 25 years of pediatric rheumatology I have only had two JRA patients that had to be hospitalized because of GI bleeding. But my experience is the same as shown in the clinical trials that about 20-30 percent of patients on NSAIDs will have GI complaints.

My hope for consideration today is that we keep in mind that we have relatively few agents that have been addressed in well-designed prospective clinical trials in children with JRA. We need a variety of agents to provide adequate treatment options for this group of patients, and

that we do whatever you feel is proper to get the information out there to those who are actively involved in the treatment of children with arthritis--the practitioners, the parents and the patients, get the information to them in some way so that they can make truly informed decisions about the care of these kids.

I thank you for the opportunity to talk about this disease that I have studied for 25 years and fought each and every year of those 25 years to help improve the outcome. Thank you.

DR. BATHON: Thanks, Dr. Lovell. We will be holding questions until after the end of Dr. Lowery's presentation.

Regulatory History, Rationale for Study of Celecoxib in Children, and Clinical Data for Celecoxib in JRA, and Overall Conclusions

DR. LOWERY: Thank you.

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I will now continue with just a brief background with regards to the context of our study of celecoxib in JRA. As I think the speakers

before have demonstrated, JRA is a relatively rare condition. We need to keep in mind that this is a pediatric population.

As Dr. Lovell showed us, previous studies with NSAIDs have been in the range of 59 patients to 432 patients and have been of durations between 8 weeks and 64 weeks. I think of note is the fact that recently approved biologic therapies were approved with only 69 patients. Therefore, in fact, our experience with NSAIDs is somewhat greater than our experience with biologic therapies.

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We studied celecoxib in JRA in response to a pediatric written request issued by the agency in January, 2002. Our objectives were to study the efficacy and safety of two doses of celecoxib versus a standard active control, and also to study the PK of celecoxib in children with JRA. We were to perform a single study that was 12 weeks in duration, 3 arms, double-blind. Subsequently all patients were to be allowed into a 12-week

open-label single-arm phase and PK assessments were to be multi-dose assessments. Patients were to be enrolled between the ages of 2-16. However, we were to enroll a percentage of patients in the younger age group, both pauciarticular and polyarticular subtypes, and also we were to enroll approximately 10 percent of systemic onset patients.

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With regards to safety, adverse events were to be collected; laboratory testing and vital signs. Development was to be assessed by the reporting of developmental adverse events. Also, because of the potential for risk to the systemic patients, these were to be particularly closely monitored. We were to study an oral formulation appropriate for pediatric use, and the information collected should provide for appropriate labeling.

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In 2002, with the written request, the study was commenced.

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The study was ongoing during 2004 in the latter part of the year, as previously discussed.

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In 2005 we completed our study in JRA at around the same time that the class warnings for cardiovascular events and the approval of meloxicam for use in JRA was issued.

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Early in 2006 we met with the FDA to agree on a proposal for the sNDA in JRA and in the middle of this year we filed, which subsequently led to this meeting today.

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Now let's review study 195, as I will call it, of celecoxib as compared to naproxen in JRA.

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Our primary objective was to evaluate the efficacy and safety of an investigational celecoxib suspension for the treatment of the signs and symptoms of JRA compared to the currently marketed suspension of naproxen. Secondarily, we were to obtain PK information to guide the dosing of

celecoxib for pediatric patients and also to collect safety information.

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As I mentioned, the inclusion criteria were 2-16 years of age. Patients were to have either course of disease. Patients needed to have at least one joint involved with active arthritis. We were to involve systemic patients. Patients were enrolled with mild to moderate disease or a minimum of mild to moderate disease and they needed to be candidates for NSAID therapy.

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Patients were excluded if they had active systemic manifestations of JRA or their disease was unstable, as manifest by recently changed DMARD therapy. For example, if methotrexate had been changed within 8 weeks; other DMARDs 12 weeks, etc.

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The study design was a parallel group 3-arm study, double-blind, double-dubbing. Patients were treated with either a lower dose of celecoxib, 3 mg/kg BID for a total of 6 mg/kg per

day; a higher dose of celecoxib, 6 mg/kg BID or a total daily dose of 12 mg/kg; or naproxen 7.5 mg/kg BID, for a total of 15 mg/kg. The double-blind phase of the study lasted for 12 weeks, as I mentioned, and then all patients had the opportunity to enroll in a further 12-week open-label phase of the study at the high dose of celecoxib.

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The primary endpoint of the study was the percent of patients who improved by the ACR Pediatric 30 response criteria, as defined by Dr. Lovell. I won't go into these measures again but just reiterate that this covers a wide variety of disease assessment, encompassing global disease activity measures and inflammation and number of joints with active arthritis.

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Secondary measures included change from baseline for each of the 6 core measures within the ACR Pediatric 30 response, and also an assessment of pain on a 100 mm VAS scale. PK was assessed, as