was safety, adverse events, clinical laboratory values and vital signs.

[Slide]

With regards to statistical methodology, a non-inferiority margin of 25 percent was set for the difference in the ACR Pediatric 30 response of celecoxib minus naproxen. Initial hypothesis testing was performed with a one-sided level at the 2.5 percent alpha, and non-inferiority was claimed if the lower limit equivalently of a two-sided 95 percent confidence interval was above minus 25 percent. With a sample size of around 75 patients we had at least 80 percent power to conclude non-inferiority.

[Slide]

The rationale for the non-inferiority margin at the time was agreed to in discussion with the FDA and also with a survey of our advisors, at the time the study was designed, with regards to what would be a minimally clinically important difference between the two active treatments. Subsequently, data has become available further

solidifying that conclusion and, indeed, we have seen that the data for the naproxen response rate is in the range of 60-80 percent. Data has become available for so-called placebo-controlled studies suggesting a range of 9-36 percent. I would point out, however, that there are no truly placebo-controlled studies in this condition. This placebo response allows other therapies, such as DMARDs and non-steroidals and other treatments in some of these studies. So, this is not a true placebo response but it is probably one of the better estimates of a range for placebo response that we have.

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With regards to baseline demographics, as requested, we did enroll a percent of patients in the younger age groups. Expectedly, the majority of patients were of female gender.

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With regards to JRA subtype, approximately half of the patients were in each of the two, pauciarticular course or polyarticular course

disease subsets. Again, as requested in the written request, a percent of patients across the 3 treatment groups were enrolled with systemic onset disease.

Not unsurprisingly given this population, approximately half of the patients were receiving DMARD or biologic use at baseline, and a majority was methotrexate. A percentage of patients were also receiving corticosteroids at baseline across the 3 treatment groups.

[Slide]

Baseline disease characteristics with regards to mean values at baseline were evenly matched across all three treatment groups. For example, the physician's global on a 100 mm scale, around 40 mm. For example, parent's assessment of function on a 0-3 scale, 0.9 in all three treatment groups.

[Slide]

In total, 242 patients were randomized evenly across the three treatment groups. Importantly, the majority of patients completed the

study, over 85 percent in each of the three treatment groups, the most common reasons for withdrawal being adverse events, lack of efficacy or withdrawal of consent.

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Moving on to efficacy, in the primary efficacy evaluation for the study, as demonstrated on this chart, the You axis represents the percentage of patients meeting the Pediatric 30 response at weeks 2, 4 and 8 and the primary efficacy evaluation at week 12. One can see that there is efficacy as evidenced by response in the order of 40 percent at week 2, with slow and gradual improvement to improvement between 60-80 percent of patients at week 12 of the study. There were no significant differences between treatments, and also the precision of effect is quite robust given the narrow 95 percent confidence intervals for the effect.

[Slide]

So, with regards to the primary non-inferiority analysis, this slide demonstrates

the difference between celecoxib and naproxen for the primary non-inferiority analysis. The vertical line represents no difference in the low dose group and the high dose group of celecoxib with the point estimates and the 95 percent confidence intervals for the difference. As one can see, for both doses of celecoxib the lower bound of the 95 percent confidence interval is well above minus 25 percent set for the lower bound to declare non-inferiority. Hence, non-inferiority can be declared for both celecoxib doses and, indeed, had the lower bound been set at minus 15 percent or even minus 13 percent both doses of celecoxib would have been declared non-inferior to the active therapy of naproxen.

[Slide]

With regards to more stringent assessments of efficacy using the ACR Pediatric 50 or 70 response, again, clear efficacy was demonstrated for both doses or celecoxib and also naproxen, with around 60 percent of patients responding using the ACR 50 and around 40 percent of patients responding

for the ACR Pediatric 70 response rate.

[Slide]

When we look at each of the 6 core measures and the percentage of patients responding by 30 percent within those, we see good efficacy across each of the 6 core measures ranging from around 70-80 percent, with some suggestion of improved efficacy at the high dose of celecoxib compared to the other two treatment groups for physician's global, ranging down for 30 percent improvement in CLP on the order of 50 percent of patients responding. The only significant finding of note was between the low dose and high dose celecoxib groups for joints with limited range of motion, which may have been in part influenced by a difference in baseline values, which I will show you shortly.

[Slide]

These are the mean values over the 12 weeks of the study for the 6 core measures, starting with the 2 global assessments, physician's and parent's. Again, we can see efficacy from 2

weeks manifest with gradual improvement to the 12 weeks improvement in all 3 treatment groups for both measuresB-the only significant finding at week 2 for the lower dose celecoxib group compared with naproxen.

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With regards to joints with active arthritis and those with limited range of motion, again there is the same pattern of effect with improvement by 2 weeks, improvement durable through to the 12 weeks of the study; significant findings between celecoxib at its lower dose compared to the high dose at week 12 for active arthritis and weeks 8 and 12 for limited range of motion. This may have been influenced by differences in baseline values.

[Slide]

Functional ability improved similarly to the other core measures, with efficacy evidence from 2 weeks of therapy through to 12 weeks. The pattern of effect for CRP was less consistent, although for all 3 treatments there was a mean

improvement for naproxen, the high dose celecoxib and lower dose celecoxib groups from baseline through to week 12.

[Slide]

With regards to the assessment of pain on the 100 mm VAS, as I mentioned, baseline scores were just shy of 44 mm and, again efficacy was evident by week 2 of treatment in all 3 treatment groups and was manifest through to 12 weeks of therapy. Mean changes fell between 40-45 mm down to below 25 mm on the 10 mm VAS during the study.

[Slide]

We conducted several subanalyses to test the robustness of the primary analysis by disease course, either the pauciarticular course or polyarticular course, for the primary endpoint the ACR Pediatric 30 response at week 12. In general, the pauciarticular patients fared a little more favorably than the polyarticular course patients, with response rates in the region of 80 percent with the exception of the higher dose celecoxib group in the pauciarticular course disease.

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Also looking at the subgroup by disease modification or DMARD therapy, in general there were no significant differences, the exception being I patients not receiving DMARD therapy at baseline between the high dose celecoxib group and the lower dose celecoxib group; conversely, a trend to reduced efficacy or less favorable efficacy in the DMARD-using patients in the naproxen group compared to both celecoxib groups.

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So, in summary of the efficacy results from the double-blind phase of the study, both doses of celecoxib demonstrated non-inferiority to naproxen for the primary endpoint of the study. Overall, the secondary efficacy analyses were supportive of the primary analysis, as were the subgroup analyses performed for disease type and also DMARD therapy.

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With regards to the safety assessment, we performed an assessment of the safety in this study

by adverse event reporting and assessment of growth by body weight and, in particular, because of known adverse effects with non-steroidals in the adult population, an emphasis on cardiorenal effects and also effects on hematologic parameters and biochemical parameters.

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Overall, adverse events were reported commonly in all 3 treatment groups, between 63 percent of patients on the low dose of celecoxib group compared to 72 percent of patients in the naproxen group. Withdrawals, adverse events and serious adverse events were reported infrequently, however, they were reported more commonly with both celecoxib groups compared to naproxen.

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Overall, with regard to adverse events, GI disorders, not unsurprisingly given the known profile of NSAIDs in both adults and children, were reported commonly, the common adverse events being abdominal pain, upper abdominal pain, vomiting, diarrhea and nausea. Also general disorders were

reported commonly although these were generally made up of reports of fever or pyrexia.

[Slide]

Also, given the population, not surprisingly, infections were reported commonly during the study. Additionally, nervous system disorders were reported commonly although these were predominantly made up of headache and reports of dizziness.

[Slide]

Again unsurprising given the pediatric population, respiratory disorders and cough and skin disorders were reported commonly during the study.

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There were 5 serious adverse events, 3 on the low dose celecoxib group and 2 on the high dose celecoxib group, and no serious adverse events were reported for naproxen. In general, these were as one would expect in this population being treated with an NSAID.

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There were 13 withdrawals in total from the study due to adverse events, 3 on the lower dose celecoxib group, 7 on the high dose group and 3 on the naproxen group. I would bring your attention to 2 withdrawals due to abnormal liver function. One patient had an increase around 4 times the upper limit of normal. One patient had an increase around double the upper limit of normal. The patient with the double recovered and there was no further follow-up information available on the patient who increased to 4-fold.

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With regards to growth and body weight, looking at mean change from baseline the mean change in body weight for all three treatment groups increased by an average of around one kilogram. Perhaps looking more specifically at the number of patients who had a decrease in body weight, one patient in the celecoxib group and one patient in the naproxen group had a decrease of more than 5 percent from baseline in body weight.

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Cardiorenal adverse effects, first looking at mean systolic blood pressure over the course of the study, there were mean increases of between 0.7 and 0.9 mmHg and 1.6 mmHg in the naproxen group. Looking at patients who had a marked increase in systolic blood pressure, defined by greater than 15 percent increase from baseline, we have used this figure. This is a typical figure used in adult populations. We see between 9, 6 and 13 percent of patients having an increase in systolic blood pressure between the 3 treatment groups.

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Serum creatinine levels changed very little during the study and there were no patients who shifted from a normal to an abnormal value on age-matched norms.

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With regards to changes in hematologic and biochemical parameters, mean hemoglobins fell in all 3 treatment groups between 1-2 g/L in the 2 celecoxib groups compared to 4 g/L in the naproxen group. With regards to patients who perhaps had a

clinically significant fall in hemoglobin by more than 10 g/L from baseline and who fell below a lower limit of normal, just 1, 1 and 2 patients had a clinically relevant fall in hemoglobin. If we assessed it at 2 I think there were no more patients.

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With regards to liver function and mean ALT changes, again, there was a slight mean increase in the 2 celecoxib groups, a mean fall in the naproxen group, patients who shifted from normal to an abnormal range. There was 1 patient in the low dose celecoxib group, you may recall, a CMV hepatitis earlier on one of the previous slides; 3 in the high dose celecoxib group. Two of those patients were the withdrawals, and no patients in the naproxen group.

[Slide]

So, overall with regards to the safety summary, gastrointestinal disorders, infections and nervous system disorders were those most commonly reported. Overall, the safety profile of celecoxib

at both doses is similar to that of naproxen. We did not see any apparent effects on growth and no developmental adverse events were reported. Small changes in mean systolic blood pressure and changes in blood pressure were seen although these appeared similar between celecoxib and naproxen. Overall, there were few serious adverse events and withdrawals from the study.

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As you recall, the study allowed patients to enroll subsequently from the double-blind phase of the study into the open-label phase of the study.

[Slid]

In total 202 patients from the original 242 enrolled into the open-label phase of the study with just the higher dose of celecoxib for a further 12 weeks and, importantly, the vast majority, over 96 percent of patients, completed the 12 weeks of the open-label phase of the trial.

[Slide]

With regards to efficacy I have just

picked out a couple of measures here but in general all the efficacy assessments through open label were consistent. Looking at physician's global assessment, we can see that the efficacy response observed at week 12 during the double-blind phase of the study was sustained through 24 weeks of therapy with celecoxib.

[Slide]

Likewise, for parent's assessment of child's arthritis pain, again, the efficacy observed through the 12 weeks of double-blind therapy was sustained through to 24 weeks of therapy.

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With regards to adverse events, overall adverse events during the open-label phase of the study were reported at approximately half the rate of those during the double-blind phase of the study. But, again, the common disorders seen during double-blind therapy were seen again during open-label therapy.

[Slide]

For example, gastrointestinal disorders with a similar pattern, general disorders, pyrexia, infections, nervous system disorders.

[Slide}

And, again, respiratory disorders had a pattern of effects similar during the open label phase of the study compared to the double-blind phase of the trial.

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There were 3 withdrawals due to adverse events in the open-label phase of the study.

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There were 4 serious adverse events during the open-label phase of the study. I will bring your attention to a case of myopericarditis associated with a flare of systemic disease at approximately 100 days of therapy into the open-label phase of the trial. The other 3, there was a non-accidental overdose and 2 infection-related serious adverse events.

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So, in summary of the open-label data the

efficacy response of celecoxib was sustained through the 24 weeks of treatment. Overall, the general safety profile observed during the open-label phase of the study was similar to that observed during the double-blind phase, and no new safety findings emerged.

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PK assessment was evaluated in 152 of the JRA patients. Of note, compared to adult patients JRA patients require higher milligram/kilogram doses to achieve similar plasma levels. This effect was not predicted ahead of study and, therefore, needs to be taken into account with regard to any dosing recommendations.

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In parallel to the study, we have been conducted a number of development activities with regards to potential formulations that could be available for a pediatric population. As outlined in the briefing documentation, the suspension used in study 195 failed for a number of technical reasons and, therefore, is unavailable for

pediatric use. We also, in parallel, investigated an oral disintegrating tablet and a chewable tablet and all of these strategies proved non-viable.

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However, through evaluation a bridging strategy based on the PK data has allowed a potential solution with regards to the problems of the non-availability of an adequate pediatric formulation. This is based on using current capsules, and an additional capsule of 50 mg for patients who are unable to swallow or who are unwilling to swallow, it can be opened and sprinkled onto applesauce, and this is not an unprecedented method of administration to children. This strategy was agreed to for submission with the pre sNDA meeting we held with the agency in January of this year. As mentioned earlier, the strategy would allow for dosing of the lighter weight children between, 10-25 kg with 50 mg BID, and for heavier patients with 100 mg BID.

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So, overall the study conclusions are as

follows: Both doses of celecoxib were as effective as naproxen in treating the signs and symptoms of JRA. The overall adverse event profiles of the agents were similar and the efficacy response to celecoxib was durable with similar response seen at 24 weeks compared to 12 weeks of therapy.

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However, before I conclude with the data it is important to review other available sources of information with regards to development and growth, general safety and cardiovascular safety from other available sources.

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We have made a thorough review of the available non-clinical data from juvenile toxicology studies focusing on development and growth where no effects were seen; a thorough review of available data from other selective COX-2; available data from adult arthritis studies and from a review of pediatric spontaneous reports sent both to us and also to the FDA. Overall, the profile of celecoxib and the predicted profile of

celecoxib in children would appear similar to other NSAIDs.

As you heard earlier, cardiovascular risks are being studied in a number of placebo-controlled studies, and in one of these studies significant increase in risk compared to placebo has been observed in the APC study. However, in both randomized, controlled trial and in epidemiologic data sets the available data demonstrate that celecoxib has a similar cardiovascular safety profile to other NSAIDs.

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We do, however, know that NSAIDs, whether they be selective or non-selective, can be associated with destabilization of blood pressure control. Approximately 4 percent of children currently, irrespective of any underlying disease, can be diagnosed with systolic hypertension based on currently accepted standards. This association of hypertension in childhood affects upwards of 40 percent of children with JRA who may take NSAIDs for long periods of time. The association of

NSAIDs and destabilized blood pressure control and the association of hypertension and adverse long-term cardiovascular risk in adults is perhaps one of the most salient points for discussion today by the committee with regards to the safety of all NSAIDs in this population.

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Of note, however, in robust clinical trials where celecoxib has been evaluated compared to non-steroidals such as naproxen for changes in blood pressureB-this was a 12 week study in diabetic patients with hypertensionB-no differences have been observed between celecoxib and naproxen with regards to effects on blood pressure.

[Slide]

So, overall with regards to safety, we have observed a similar tolerability and safety profile. The available data from use in children has not identified unique safety concerns. We have observed risk compared to placebo in one study with regards to MI, CVA and CV death, but there is no evidence of increased cardiovascular risk for

celecoxib compared to other NSAIDs. All these agents are associated with changes in blood pressure control.

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Hence, there are some unknown risks. The size and duration of our study was unable to exclude the risk for rare events or latent toxicity beyond the 6 months of treatment. Also, the long-term sequelae of treating patients with JRA, perhaps over many years, with disturbance of blood pressure and long-term cardiovascular morbidity and mortality is unknown. However, this unknown risk is applicable to all NSAIDs whether they be selective or non-selective.

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To this end, we have put in place already a robust pharmacovigilance and management plan to assess the ongoing safety, tolerability and toxicity of celecoxib. This includes spontaneous reporting using enhance data capture for cardiovascular events. Also, continuous assessing severe cutaneous adverse reactions, the severe

reactions to the skin which have been associated with this class of drugs.

As I mentioned earlier, we are fully evaluating the long-term cardiovascular risks of celecoxib in the PRECISION trial in an adult population. Co-sponsored with the NCI, a study is starting currently examining a pediatric familial adenomatous polyposis study, with patients between the age of 12 and 17 being evaluated for 5 years with high dose celecoxib compared to placebo, which will provide some additional information, albeit in a different patient population.

Irrespective of the outcome of this meeting, we will also be putting in place more robust monitoring of pediatric reports to the institution of a pediatric expert panel to provide better information on causality assessment and associated therapy with celecoxib from any reports to identify unexpected or rare events in this population.

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So, my overall conclusions: Celecoxib

demonstrated efficacy non-inferior to naproxen, and met the requirements of the pediatric written request to inform physicians on appropriate use, labeling could range from minimal information to approval of the indication. Underscoring this is the data we have created to date and the data we will create important to inform prescribers of the relative benefits and risks of celecoxib in treating JRA.

JRA affects many thousands of children. It is characterized by pain, inflammation and impact on function and there is a medical need for NSAIDs. To date there is no identified unique safety concern with celecoxib in this population and there may be unknown risks of treatment shared by all NSAIDs.

Thank you for your attention. I believe we are taking questions.

DR. BATHON: Right. Since we have used the whole hour for your presentation and we want to stay right on time, we are going to move on to the FDA presentation next. But in the afternoon

session we will have plenty of time for questions that can be addressed to Pfizer at that time. Our next presentation is by Dr. Jeff Siegel from the FDA.

FDA Presentation

Risk/Benefit Profile of Celebrex for Use in JRA

DR. SIEGEL: Good morning.

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In my presentation I will be reviewing for you the overall risk/benefit relationship for celecoxib in children with juvenile rheumatoid arthritis.

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As you have heard, juvenile rheumatoid arthritis is a serious chronic disease. Treatment has also been reviewed for you. It involves treatment with non-steroidal anti-inflammatory drugs, or NSAIDs, for their anti-inflammatory and analgesic effects. For more serious disease children are treated with corticosteroids and disease-modifying drugs. Physicians commonly have to try a variety of NSAIDs before they find one

that is tolerated and that provides adequate pain relief for these children and additional options for pain relief is an important goal.

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Since most drugs have at least some side effects, assessing utility of a new drug involves weighing the benefits against the risks. To assess the potential benefits we generally look at the available clinical trial data. To assess risks we use a variety of sources of information including clinical trial data, post-marketing information and other information that is known for products in the same class.

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In my presentation I will review the efficacy data from the trial of celecoxib in JRA. You have already heard in general terms and in much detail about the trial of celecoxib in JRA from the sponsor. So, I will be restricting my comments to specific issues regarding design and the results. I will be specifically focusing on some limitations of this type of trial design and what conclusions

we might reach from it. Then I will review the safety data. I will discuss the results from the celecoxib trial in JRA. I will discuss the data that are available from post-marketing information, and I will also discuss concerns based on other information we have for COX-2 selective and COX-2 non-selective NSAIDs.

[Slide]

First turning to efficacy, as you have heard, the trial of celecoxib in JRA was a randomized, double-blind, active-controlled trial that compared celecoxib at 2 doses, 6 mg/kg/per day or the high dose of 12 mg/kg/day with naproxen 15 mg/kg/day. There was initially a 3-month randomized, blinded phase that was followed by 3 months of the open-label phase where children received celecoxib 12 mg/kg/day. The trial was designed to exclude non-inferiority of celecoxib to naproxen.

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So, what is a non-inferiority design and how are these studies carried out? Well, what we

would like to know is whether the new drug is just as effective as the active comparator drug. In practice, we can't ask the question quite this way. Instead, we ask whether the new drug is inferior to the active comparator to an extent that exceeds some very small non-inferiority margin.

What is shown here is the way a trial like this is done and how it is analyzed. Shown up here are the point estimates for the active comparator. For example purposes, here it is chosen as 60 percent. With the study drug it is just shown as being slightly below that. These bars around the point estimate are the 95 percent confidence interval. But this means that if you were to do this study many times you would find a range of estimates for the proportion of responders and this provides an estimate of what that range would likely be, and this is the 95 percent confidence that the actual result would be within this range. So, it is shown for the active comparator and the study drug here.

So, the way you assess non-inferiority is

that you subtract the results for the active comparator from the results of the study drug. Since, in this example, the study drug is slightly below the difference is slight below zero, so a small margin inferior to the active comparator.

Then you look at the 95 percent confidence interval and you look to see whether the lower bound of the 95 percent confidence interval is below the non-inferiority margin. So, here the margin is shown as 25 percent and the 95 percent confidence interval clearly shows that it showed non-inferiority. Any non-inferiority was less than the pre-specified 25 percent margin in this example.

[Slide]

In the celecoxib JRA trial the primary endpoint is the JRA definition of improvement 30 that measures improvement in a composite of these individual components, as you have heard. The physician and parent/patient global assessment, assessment of function, the number of joints with active arthritis, number of joints with limited

range of motion and the C-reactive protein. As you heard, the trial met the pre-specified endpoint excluding a non-inferiority margin of celecoxib to naproxen of 25 percent.

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So, the question is does this study result clearly demonstrate efficacy of celecoxib in JRA? Well, the FDA reviewed the trial design and agreed that it was in general terms acceptable. There are, nonetheless, concerns about the conclusions that can be reached from the study.

Inferring efficacy of celecoxib from the study results requires making a judgment about the adequacy of the pre-specified 25 percent non-inferiority margin. If we believe that the 25 percent margin is too large, then the statistical demonstration of non-inferiority may not by itself allow a determination of efficacy.

[Slide]

Inferring efficacy in a trial that compares drug to an active comparator requires making an assumption about how placebo-treated

patients would have done if a placebo arm had been included. The non-inferiority margin is set to make sure that the drug is efficacious, that is, that it retains some portion of the effect size of the active comparator. For example, if the placebo response is expected to be, say, 30 percent and the active comparator is expected to be 60 percent, then the margin could be set at 15 percent, which is half of 60 percent minus 30 percent, or 30 percent, and this would allow you to reach the conclusion that the study drug retains at least half the effect size of the active comparator.

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So, there are two methods that are used in general for setting inferiority margins in this type of trial. In the first you review all placebo-controlled trials of the active comparator using the endpoint that is chosen and set the margin at some portion, say 50 percent, of the effect size that was determined from these placebo-controlled trials. The effect size here is defined as the response to drug minus the response

to placebo.

In some cases this rigorous method can't be used and a different method is used where the margin is set on some clinically ignorable margin. This is the method that is used, for example, for renal transplant trials where the margin is often set at 10 percent when comparing drug to a calcineurin inhibitor.

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So, what was used for setting non-inferiority for celecoxib and what methods are available for setting this margin? Well, for a JRA trial using naproxen as an active comparator you can't use placebo-controlled trials to set a margin because no placebo-controlled trials with naproxen using this endpoint are available.

Employing the second method to set the margin requires making an assumption about the effect size of naproxen. For example, if the effect size is 50 percent, then a 25 percent margin would exclude loss of half the effect. If the effect size is 25 percent, however, then a 25

percent margin would not distinguish an effective drug from an ineffective drug.

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So, what data are available on placebo responses using the JRA DOI 30? Very few data are available using placebo-controlled studies that use the JRA DOI 30 in a prospective manner. However, we do have data from one placebo-controlled 3-month trial of infliximab that was reported last year at the American College of Rheumatology meeting. This placebo-controlled trial showed a placebo response rate of 48 percent. If we assume a placebo response rate in the celecoxib trial of 48 percent, then the 68 percent response rate with naproxen would imply an effect size of 20 percent. Of course, other assumptions for the placebo response would provide different estimates for the naproxen effect size.

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So, what are the implications? Well, clearly, depending on the assumptions for th effect size of the active comparator the 25 percent

non-inferiority margin that was chosen may be too large. If the pre-specified margin is inadequate, then it is necessary to consider the totality of the data to judge whether the trial demonstrated efficacy of celecoxib.

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What are some other data we have? Well, there are a couple of sources of information. One is in the JRA trial. The response rate for celecoxib at the 6 mg/kg dose was 69 percent and this compared to 68 percent for naproxen. Statistically, this excludes non-inferiority of 13 percent.

In addition, a higher response rate with celecoxib 12 mg/kg/day was seen. This is informative but this is not the dose that is proposed for marketing. In addition, higher doses of celecoxib in adults have been shown to be less safe than lower doses in longer-term trials.

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In summary, celecoxib 6 mg/kg/day met the pre-specified endpoint excluding a 25 percent

non-inferiority margin. Depending on the effect size assumed for naproxen, the 25 percent margin may not be optimal. Therefore, assessment of efficacy depends on evaluation of the totality of the data.

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I am going to turn now to an assessment of the safety profile of celecoxib.

[Side]

As you have heard, 242 children were enrolled in the randomized portion of the celecoxib trial in JRA and they received celecoxib 6 mg/kg/day or 12 mg/kg/day or naproxen 15 mg/kg/day for 3 months. And, 202 children enrolled in a subsequent 3-month open-label phase and received celecoxib 12 mg/kg/day for an additional 3 months.

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At the dose proposed for marketing in study 195 the most common adverse events were GI, infections and infestations and nervous system disorders. Respiratory disorders, eye disorders and metabolic disorders were seen more frequently

with celecoxib 6 mg/kg/day than naproxen. Overall, however, common adverse events were similar in type and frequency to those seen with naproxen.

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Turning to serious adverse events in study 195, those seen more frequently with celecoxib included GI disorders, including upper abdominal pain, pyrexia and musculoskeletal, connective tissue and bone disorders. Skin reactions and allergic reactions were also observed. Overall, the serious adverse events and severe adverse events seen in children receiving celecoxib represented events seen in this patient population and events known to be associated with other NSAIDs.

[Slide]

The agency reviewed post-marketing reports in children receiving celecoxib, and this review showed no new safety signals for the small number of adverse event reports received from children receiving celecoxib off-label.

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I want to talk just a little bit about some of the toxicologic findings. Two juvenile animal models were carried out, repeat-dose toxicity studies. One was a 7-week study initiated in 7-day old rats. The other was a 5-month study initiated in 10-week old dogs. No toxicity was seen with respect to growth or development, as you have heard. However, increased sensitivity was seen to gastrointestinal events, namely, ulceration with peritonitis, and skin effects, namely, cutaneous and subcutaneous ulcerations, compared to previous toxicities in adult animals.

The no-effect level seen in the juvenile animal studies with respect to these events provide a margin of safety for clinical use in pediatric patients. Just for those not expert in toxicology, the no-effect level is the dose of the drug where no adverse events were seen. So, these adverse events that I described were seen at higher levels and we do have a margin of safety with respect to the doses that are used in children.

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Looking at the effects of celecoxib with respect to the reproductive tract effects, in the juvenile rat study there were certain findings, as shown here. Unilateral or bilateral enlargement of the testes and prominent tubules in the epididymal fat pad was seen, and there was microscopic evidence of spermatocele and minimal to slight unilateral or bilateral dilatation of seminiferous tubules and epididymal hypospermia in all the celecoxib-treated groups.

Of note, similar findings were seen in a single control rat in the study, and there was no dose response seen in the rat. These findings were not observed in the juvenile dog or in adults of either species. The clinical implications of these findings are still under review at the agency.

[Slide]

To fully explore the safety of celecoxib in children it is important to look at the known averse events associated with the NSAID class. These include cardiovascular toxicity, GI toxicity, fluid retention, edema, renal toxicity, hepatic

enzyme elevation and bronchospasm in patients with aspirin-sensitive asthma.

One case of liver enzyme elevations was seen in study 195 and one case of severe asthma was seen. Overall, these adverse events did not seem to be seen at a rate that was clearly higher than what was seen with naproxen.

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Risk of GI bleedingB-the COX-2 selective class of NSAIDs was originally developed to reduce the life-threatening GI bleeds that are seen in adults treated with NSAIDs. While celecoxib was shown to reduce GI ulcers endoscopically, the CLASS study did not show reduced risk of clinical GI bleeds with celecoxib. In children GI bleeding is a very uncommon adverse event with NSAIDs.

[Slide]

As you have heard, data indicate an increased risk of cardiovascular thromboembolic events, in particular myocardial infarction, in adults treated with COX-2 selective NSAIDs, including celecoxib. The risk of cardiovascular

events with non-selective NSAIDs is not clearly less than that seen with COX-2 selective NSAIDs.

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In children, given that it is primarily adults who are at risk for cardiovascular thromboembolic events, these events were not expected in the celecoxib trial in JRA and, indeed, none were observed.

However, the long-term risk for children with celecoxib is unknown and cardiovascular risk is a potential concern in children with JRA in view of a couple of considerations. One is that we have seen a risk of accelerated atherosclerosis in adults with inflammatory rheumatic disease, for example lupus and rheumatoid arthritis. In addition, there is recognition that increasing numbers of children have risk factors for cardiovascular disease such as obesity, hypertension, hyperlipidemia and type 2 diabetes.

[Slide]

So, in summary, overall the risk of adverse events was similar in children receiving

celecoxib in the clinical trial as in children receiving naproxen. Overall the safety profile in study 195 was similar to that known in the NSAID class.

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In assessing the risk/benefit ratio for celecoxib in JRA it is important to consider the observed safety profile of celecoxib in JRA, the known risks of NSAIDs in this patient population and potential long-term risks based on our knowledge gained from studies in adults. Given the potential risks, it is important to consider the need for new NSAIDs in children with JRA to supplement products that are currently available.

Thank you, and I will take any questions.

DR. BATHON: We have a few minutes for questions. In the absence of any questions, we will take a short break. We will reconvene here at 11:00 o'clock for the open public hearing, 11:00 o'clock sharp.

[Brief recess]

DR. BATHON: Let's take our seats. I am

going to read a statement before we begin our open public hearing and then we will proceed with our first speaker.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: Thank you. Our first speaker is Vincent DelGaizo.

Open Public Hearing

MR. DELGAIZO: Thank you for the opportunity to speak here. Nobody paid for me to get down here or be here today.

I wanted to tell you that at six months old my son was diagnosed, after staying in an intensive care unit for about a month, with systemic onset arthritis. He was treated initially with intravenous steroids and he was so sick at the timeB-just to kind of explain it, his white count was around 54,000. I found out a few years later that he set the record for my son's doctor for the highest white count she has ever seen.

So, a few months later he was home on 65 mg of steroids, methotrexate and Naprosyn, the maximum doses of everything. I heard somebody

saying something about 1 mg/kg of steroids. He was about eight times that. He was up around 21 hours a day, I think from the steroids but I am not sure. My wife used to bring him downstairs in the morning after a warm bath, sit him in a high chair and he used to sit literally for hours with his arms up in the air, like this. It is an image that will be burned in my mind forever.

I remember being at work and calling her every hour to ask if he put his arms down yet; if he put his arms down yet, and she would say, no, not yet; no, not yet. Then, after a few hours he would finally be able to straighten his arms.

After a few weeks of this a decision was made by my wife, myself and his doctor to try something else because his current drugs weren't working. So, we tried him with Celebrex and approximately three or four days later he put his arms down and he started to get better.

I don't know too much about what goes on inside of his body. I don't know if it was the steroids. I don't know what happened. I don't

know if it was God. But something definitely happened for him to start getting better. Maybe he just was tired of being sick. My son is a triplet. If you saw him today--really the most powerful thing I could have done was to bring all three of them here and none of you would be able to recognize, other than his doctor, which child has arthritis. He plays T-ball. He plays soccer. He plays tennis. He swims. He ice skates. He is a very active kid. He is tall. He is doing fabulous!

And, the real reason why I am here today is because I think everyone understands that there is no magic bullet with this disease. There is nothing-Byou have to try a lot of different things to find something that works and, as parents, we need options. We need to be able to try different things because sometimes what everybody else is using doesn't work out that well. Really the dosing of itB-my doctor had the courage to use it and the expertise to dose it. Somebody was saying that two-thirds of the kids don't see a specialist

so that is two-thirds of the population that have this disease and the doctor doesn't know how to dose the medication like this without somebody like the FDA. I think that is pretty important.

I am not here for my son. I am here for other children because my son can get access to the medication. He got it at 18 months old. You know, he will get it again if he needs it. That is pretty much all I have to say.

MS. CLIFFORD: Thank you very much. Our next speakers are Kathy and Lacey Whatley.

MS. L. WHATLEY: Hi. I am Lacey Whatley, from Birmingham, Alabama. At the age of 10 months I was diagnosed with polyarticular JRA. I am now 17 and practically my whole life I have been on what most people would consider adult medication. I have tried gold shots, Enbrel, just to name a few but, unfortunately, these would work for a while and then become ineffective. As long as I can remember I have been on methotrexate injections or pills and I am now currently on Remicade infusions every month.

But what I am really supposed to be talking about today is the Aleve that I take twice a day for pain. On December 19 I will be having a total hip replacement and the doctors have told me that I will not be able to take the Aleve a week before or after surgery. It is my understanding that if I were allowed to take Celebrex I would be able to take it up to the day before surgery and continue it soon afterwards because, unlike Aleve, it will not cause bleeding and sometimes I get bloody noses from all the Aleve that I do take. So, whether it is an over-the-counter drug or a prescribed drug, my doctor, my parents and I have discussed all the medications that I take and we really think I would benefit from Celebrex, and we would love to have that as an option for me.

MS. K. WHATLEY: I am Kathy, Lacey's mother. When she was ten months old I put her on Pediaprep. Her father and I studied all the pros and cons of that medicine. Then when she was three and they wanted to start gold injections, of course, we studied all the pros and cons of those.

In fifth grade when she went on Enbrel we learned the side effects of that drug.

I need you to know we have done that with Celebrex. I have talked to her pediatric rheumatologist, her rheumatologist in Birmingham, our pharmacist, physicians that are friends, friends that take Celebrex and we have come to the conclusion that it would be a good option for Lacey in handling her pain because I don't think what she takes now is as effective.

In light of the fact that she does face a hip replacement on the 19th and, by the way, we talked to four different orthopedist surgeons at four different hospitals and we don't make any of these decisions lightly. You need to know that we go day by day when you are talking about the pain. The fact is the week before her surgery there will not be any medicine for her and she will be in a great deal of pain. She will have trouble getting out of bed. She won't be able to shower by herself. But if we could give her the Celebrex up to the day before to help with pain, that would be

huge.

I mean, I think it is quite sad that I am standing here before you, talking about giving my child drugs and it is quite sad that what she wants for Christmas is a hip replacement. But this is an aggressive, crippling, painful disease. So, her father and I have learned that we have to be aggressive and speak out for what we want, and we have studied Celebrex and we believe that before her surgery and after her surgery it could help her control the pain of juvenile rheumatoid arthritis.

MS. CLIFFORD: Thank you.

MS. K. WHATLEY: And we would like to have that option.

MS. CLIFFORD: Dr. Earl Brewer?

DR. BREWER: I am a retired pediatric rheumatologist, 16 years. I remember this committee 30 years ago, from 1976 to 1980. We set forth the guideline for studying non-steroidals, which is kind of interesting; it is a full circle. I am impressed with the sophistication of everything. This room is much better than that

dreadful basement over in the Parklawn Building. You can breathe here.

But I am here as the old guy for the children. To reinforce what has been said so well before by physicians, children do need relief of pain of rheumatoid arthritis. They do need relief of inflammation. One size does not fit all. They need options. So, I think this consideration here is another option for the children with severe arthritis.

MS. CLIFFORD: Thank you so much. Our next speaker is Dr. Balu Athreya. He is speaking on behalf of the American Academy of Pediatrics and the American College of Rheumatology.

DR. ATHREYA: Good morning. I am Dr. Balu Athreya. I am honored to be present here on behalf of the American College of Rheumatology, not the Academy of Pediatrics. The American College of Rheumatology is an organization of physicians, health professionals and scientists that advance rheumatology through programs of education, research, advocacy and practice support that foster

excellence for people with arthritis and rheumatoid and musculoskeletal diseases.

I am a pediatrician and a pediatric rheumatologist, and I am a past chair of the executive committee of the section on pediatric rheumatology of the American College of Rheumatology. We want to convey to you today that juvenile rheumatoid arthritis is the most common form of chronic arthritis in children. It causes pain, disability and can be crippling. It interferes with school attendance and business and work for parents.

Non-steroidal anti-inflammatory drugs have been a mainstay of treatment for these children for the past 30 years with JRA. The Physician's Desk Reference lists 22 approved non-steroidal anti-inflammatory drugs for the treatment of rheumatoid arthritis, of which only five drugs are licensed for use in children with JRA. Many of these drugs require dosing two to four times a day and have limitations in their tolerability, particularly with considerable gastrointestinal

toxicity.

Pediatric rheumatologists and the children they treat need additional options for safe and effective medications specifically approved for the treatment of JRA. These medications need to be child-friendly in terms of dosing and the side effect profiles.

In labeling drugs for use in rheumatoid arthritis we need to keep in mind that children are not small adults. The data obtained from adults cannot automatically be extrapolated to children. Dosing and pharmacokinetics often differ between children and adults and the side effects seen in one population may not apply to the other. There should be an increased emphasis on studying drugs that offer a promise of improvement in dosing, efficacy and safety for children with JRA and in monitoring their long-term safety after licensure.

We hope that the pharmaceutical industry and FDA can work towards the goal of developing and licensing more medications, including non-steroidal anti-inflammatory drugs that can be safely used for

children with arthritis. Thank you.

MS. CLIFFORD: Thank you, Dr. Athreya. Our next speaker is Dr. Gloria Higgins.

DR. HIGGINS: I am honored to be here today to present to you a recent survey of pediatric rheumatologists to determine usage and experience with Celebrex. You were already shown information about a CARRA survey that was similar that occurred a couple of years ago. Because the awareness of potential side effects with the COX-2 inhibitors has been increased by events over the last couple of years a group of us independently got together and decided that we should repeat essentially that survey, with a little bit of variation, to determine if any new toxicity signals have shown up. This was independently generated and subsidized, and I would like to say that I have no financial or other kind of relationship with Pfizer. I have not participated in any trials sponsored by Pfizer, although I have participated in trials sponsored by Merck, Amgen and Abbott.

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This was generated to be an on-line survey using the SurveyMonkey Service and it was conducted during this month, November, 2006. It consisted of 15 questions. The respondents could be anonymous or could sign, by their choice. We solicited responses from U.S. pediatric rheumatologists either on the pediatric rheumatology list server, which is a bulletin board that many of us use and also sent individually by email to all the pediatric rheumatologists who were listed in the ACR directory.

Because of the wide reach of the list server and the fact that not everybody looks at it all the time, we really don't know how many people received the survey but we know that at least 150 did, based on the number that were received from the ACR directory.

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The responders consisted of 86 Board certified pediatric rheumatologists, 11 Board eligible, and 6 who were practicing pediatric rheumatology but who were not Board eligible or

certified. There are some people who do not fit with the new rules for Board eligibility who have been seeing children for a very long time. The mean years in practice was 14.6, with a range of zero for two fellows who responded to 43 years. The total was 1,504 physician years which, as you see, is very similar to the total physician years in the CARRA survey. The distribution was in 35 states and one U.S. territory.

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These were the questions that were asked: Do you consider that COX-2 drugs are important for treatment of JRA? Of the 103 respondents, 95 said yes; 8 said no. Similarly, 95 had used Celebrex and 8 had not. Of the people who thought that there were some advantages to the COX-2 inhibitors, 85 people cited fewer adverse effects; 27, easier dosing; 5 thought that there was increased efficacy and that is compared to 8 who thought that there was no advantage; and 16 cited other issues, such as better GI tolerability, lack of anti-platelet effects, lack of bruising, etc.

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The source of the information was by estimate on 91 responders. Two actually had a chart review and the rest did not answer what their source was. As far as the numbers of patients treated with Celebrex, 94 people responded and, as you can see, some people had treated many patients and some had not treated very many. The total Celebrex exposure, which is estimated, is between 1,000 and 2,000 patients.

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The average duration of Celebrex treatment, 82 people responded to this. As you can see, the sort of median range of exposure to Celebrex has been around 7-18 months, some people less and about a quarter of the patients treated for over 18 months. I think this goes along with what some of your panel has talked about already this morning.

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We asked the people when they have chosen Celebrex and 95 responders answered and more than

one answer was possible so the numbers add up to more than 95, as you can see. The predominant reason was if there was toxicity with another NSAID. Other reasons were after failure with one or after more than one NSAID. Then, among the other reasons, again, patients who have gastrointestinal disorders, such as inflammatory bowel disease along with their arthritis, gastritis, etc.; patients who have thrombocytopenia or coagulation deficits; and also some of these physicians considered it to be safer in patients with asthma.

I would note, related to the asterisk here, the failure with more than one other NSAID was cited by many as an insurance issue because insurance often requires that you try two other NSAIDs before they would consider authorizing Celebrex. So, in that way, because the drug is not labeled for JRA, there is some restriction to access.

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Then we asked about adverse effects. Of

95 responders, 83, which is 87 percent of the physicians, had seen adverse effects. Then we asked did the adverse effects or toxicities differ from the other NSAIDs and 84 percent of these said no; 16 percent said yes. Of the ones who said yes, actually the thrust of it was that their perception was that the toxicity was less, less GI toxicity especially and less bruising.

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To the question of whether there were any vascular thromboses or cardiovascular toxicities in JRA patients treated with traditional NSAIDs, 95 responded. Only one person had seen this in their years of practice, which was a patient who had the underlying condition of thoracic outlet syndrome who developed a deep venous thrombosis on naproxen. None of the 94 responders had seen a cardiovascular adverse effect with Celebrex in JRA patients.

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So, to summarize, NSAIDs are frequently used in the treatment of JRA, as we all know. We

realize that this survey is limited because it is not randomized, double-blind, placebo-controlled, prospective. It is just an estimate from pediatric rheumatologists. But I have to tell you that we, as a group, are a pretty darned careful, thoughtful and thorough group and I think with our awareness raised we really would have noticed some cardiovascular stuff going on.

COX-2 inhibitory drugs are perceived by most pediatric rheumatologists as being important for the treatment of JRA and Celebrex has been used mainly in cases of treatment failure or toxicity to other NSAIDs in the pediatric rheumatology population. Celebrex typically is used for what I would call relatively short periods of time. The median durations were between 7-18 months.

At least from our practice-based survey, it appears to have similar adverse effects or toxicities in children as other NSAIDs, and the perception among us is that it is associated with less GI toxicity and less hemostatic problems. Thank you.

MS. CLIFFORD: Thank you, Dr. Higgins. Our next speaker is Dr. Patience White, from the Arthritis Foundation.

DR. WHITE: Good morning, Dr. Chairman and the members of the committee. My name is Patience White. It is a privilege to appear before you this morning in my capacity as a chief public health officer of the Arthritis Foundation and a practicing rheumatologist.

At the outset let me advise you that I do not have any direct financial or other relationship with the applicant company, Pfizer. My employer, the Arthritis Foundation, accepts charitable contributions from a wide variety of sources including Pfizer but none of these grants involves the matter before the committee today, nor have I had any contact with the company in connection with this application.

As you may know, for nearly 60 years the Foundation has been a leading voice for people with arthritis, now numbering over 46 million Americans including an estimated 300,000 children. We

believe it is critical for the Foundation to be an active participant in government actions that will impact the lives of our constituents, a condition that is certainly met by this panel's responsibilities. At the same time, I appreciate the duties of the panel, having served on it from 1988 to 1992 and chaired it from 1990 to 1992. Your job I think has only gotten more difficult since that time with the surge of new therapies to be reviewed and the rising public and congressional pressure to guarantee safety while ensuring appropriate access to treatment options.

In fact, I can't imagine any situations where the committee would be in a more obviously visible situation than you are today. As everyone knows, the COX-2 class of therapies has been the focus of some of the most intense regulatory and media attention of any product in the past decade. While most of this pressure has centered on Vioxx, it would be naive to think that an application for a pediatric indication for another product in this class, Celebrex, would receive anything but the

most thorough scrutiny on all fronts.

Let me say clearly at this point that the Foundation is not in a position to comment specifically on the applicant's supporting data or the drug itself. Fortunately, there are many perspectives before the committee today to inform these questions. Instead, our views today center on important patient- and consumer-driven perspectives that are relevant to the committee's work.

Let me be specific. First, while we deeply respect the need to protect patient safety, the Foundation firmly believes that there must be a balanced approach to weighing the risks and benefits associated with any therapy. Recent years have seen the approval and delivery of several important pharmaceutical and biological therapies for treating various forms of arthritis. Many of these therapies have significantly improved the lives of people with arthritis, both adults and children.

In that regard, we strongly urge the

committee to consider the risks of the disease itself when determining its recommendations. While any therapy will have various characteristics impacting efficacy and safety, one thing that is absolutely unquestioned about juvenile rheumatoid arthritis is the pain and disability which are visited upon children with this ravaging disease.

Second, the Arthritis Foundation believes that patients need a wide range of therapeutic options to appropriately manage the pain and disability of arthritis. We all know that not every therapy is effective for every patient even within the same class. But pain relief for people of all ages with arthritis, including children, is critical. We are supportive of your efforts to ensure that the widest range of safe and effective products are available to patients who suffer from this debilitating disease.

In closing, let me thank the committee for its hard work and commitment to advancing the therapeutic options for people with arthritis, including adults and children. Please be assured

that the Foundation is prepared to be an active partner throughout the process of developing and assessing the widest range of therapies. In particular at this time, we are committed to helping the committee fill its positions for consumer and patient representatives. We believe these voices are essential to the process. Thank you again for this opportunity to testify this morning.

MS. CLIFFORD: Thank you, Dr. White. Our next speaker is Dr. Brandt Gro.

DR. GROH: Brandt Gro., pediatric rheumatologist and associate professor of pediatrics at Penn State Children's Hospital.

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I appreciate this opportunity to address the committee. I am going to present some survey data from Dr. Deborah Levy and also Dr. Lisa Imundo, both assistant clinical professors at Columbia University Medical Center. This is data that was presented on a poster at ACR meeting, just recently, published, as you see there, in Arthritis

and Rheumatism. This research was funded by an unrestricted grant from Pfizer. I personally don't have any connections with Pfizer.

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The poster title is "Practices and Concerns of Pediatric Subspecialists." This survey was an internet survey. The way this was done is, first of all, random samples were generated from professional organization membership rosters. Then these people were invited by email to log onto a website to complete the survey. Of 1,289 invitations, there were 338 respondents. Of those, 8 were dropped in that 2 of these respondents only saw patients greater than 18 years of age and 6 never used NSAIDs at all. There you can see the breakout of just who was involved in the survey, 165 pediatricians, 99 pediatric rheumatologists -Bagain, this is all of North America--42 pediatric orthopedists and 24 pediatric surgeons. The response, by the way, was 28 percent.

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This is a figure I borrowed from the

poster, COX-2 versus traditional NSAIDs: perceived differences. I will just briefly point out that 40-60 percent of survey respondents--by these various measures listed over in the legend, safety, pain, inflammation, tolerabilityB-rated that these two classes, the COX-2 specific inhibitors and traditional NSAIDs, were equally effective. Moving over to the next set of bars, fewer respondents rated the COX-2 selective inhibitors as being more effective, but the one domain that stood out was tolerability, the higher purple bar at 44 percent.

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This is a little bit more complicated, another figure from the poster that reviews NSAID prescribing frequency for specific indications. If you ignore the grey part of the bar on top, that gives you the percent of physicians who ever prescribed COX-2 inhibitors for these various indications. I will just point out that as you go from left to right, of those prescribing COX-2s 82 percent have ever prescribed those medications for arthritis. Then, scanning over further, the next

highest percentage is 61 percent ever prescribed for musculoskeletal pain, and further to the right, the next highest is 37 percent for soft tissue injury.

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The following table is based on selecting out just the 99 pediatric rheumatologists, and that is almost all of us actually. There are about 200 of us in the U.S. Then, surveying the side effect profiles, comparing again traditional non-selective NSAIDs to the COX-2 inhibitors and looking for things that pop up as significantB-and, again, these are various subjective impressions. This isn't necessarily based on chart reviews performed by all of these survey respondents, but abdominal pain does come up as a significant difference, or at least the impression of a significant difference, as does epistaxis, easy bruising, headaches and fatigue, all in favor of the COX-2 selective inhibitors.

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On the flip side, looking at those

physicians who never had prescribed COX-2s, this is how they break out by specialty. Fifty percent of physicians surveyed overall had never prescribed COX-2s and that comprised 72 percent of pediatricians. Within the group of pediatricians, however, some of them were primary care, the majority, and some of them specialists. Then, 39 percent of pediatric surgeons never prescribed COX-2s; 50 percent of pediatric orthopedists and only 4 percent of pediatric rheumatologists. So, you can clearly see that most of the COX-2 usage is in the orthopedic and rheumatology communities.

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In summary, the authors of this survey concluded that traditional NSAID and COX-2 inhibitor use is perceived as safe by most pediatric physicians. A few non-rheumatologists prescribe COX-2 specific NSAIDs for their pediatric patients but, again, pediatric orthopedists and pediatric rheumatologists would be the most frequent prescribers. Fewer side effects were reported with the use of the COX-2 specific NSAIDs

in this survey. There are some barriers to prescribing NSAIDs or COX-2 specific NSAIDs, which is that figure I skipped over, those being mainly lack of a liquid formulation and lack of a single daily dose schedule. Then, perhaps most importantly there were no significant cardiac side effects or thromboses, reported in this survey. Thank you.

MS. CLIFFORD: Thank you, Dr. Gro. Dr. Kathleen Haines?

DR. HAINES: My name is Dr. Kathleen Haines.

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I am a Board-certified pediatric rheumatologist in a hospital-based practice at the Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center, Hackensack, New Jersey. I am a member of both the American College of Rheumatology and the American Academy of Pediatrics. I have just finished serving a term on the executive committee of the section on pediatric rheumatology of the AAP, but I am here today as a

pediatric rheumatologist, not as a representative of any organization. I have not participated in any studies sponsored by Pfizer. I have no association with celecoxib as a drug. I have, however, participated in clinical studies sponsored by Regeneron, Amgen, the FDA's Orphan Drug Program and the NIH. I am here today to show you data that I received from my colleague, Dr. Beth Gottlieb, regarding the pediatric rheumatology community's experience with COX-2 inhibitors in children. It is my understanding that Pfizer has had access to this data, and I also understand that Dr. Gottlieb has a consultant agreement with Pfizer. However, the collection of this data was not sponsored by Pfizer. Dr. Gottlieb, myself and other members of the pediatric rheumatology community were not aware whether Pfizer was going to present any of this data today so we wanted to make sure that you saw it because we think it is important.

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The study that Dr. Gottlieb was the

principal investigator on was called the long-term outcome study of children with juvenile rheumatoid arthritis. It was a prospective observational, multi-center study of children with JRA and they were enrolled at the onset of their disease. The purpose of the study was to collect data on outcomes of the various treatments used by pediatric rheumatologists. It was a non-interventional study, and the support for the study was obtained from the Arthritis Foundation.

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The rheumatologists who participated in this study got IRB approval at each of their local sites. They enrolled patients within six weeks of diagnosis. The treatment was initiated at their site according to whatever the treating physician's usual practice was. There was no specified treatment in this study. At the enrollment of the patient and on an annual basis, data was collected including physical exam, what treatments had been given over the year, side effects of the treatment, and outcome measures were recorded and then sent to

the study coordinating center.

There were two cohorts available for this study. Cohort 1 was diagnosed between 1996 and 1999. This was data collected by Suzanne Bowyer of the James Whitcomb Riley Children's Hospital in Indianapolis, Indiana. Suzanne had started the study and in 1999 she handed the database over to Beth who then got funding to continue it from 2001.

Cohort 2 was diagnosed from 2001 to the present and this was collected by Beth Gottlieb, at Schneider's Children's Hospital in New Hyde Park, New York, which I believe is an affiliate of Albert Einstein College of Medicine.

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There were 1,115 patients in the database, and that is from both cohorts. Sixty percent of the patientsare pauciarticular JRA; 32 percent are polyarticular JRA and 8 percent are systemic onset JRA; for 35 percent of patients she could not decide what they were classified as. Of over 1,000 patients, 588 had data that could be evaluable on their NSAIDs, 58 of them to the COX-2 inhibitor,

and it was either rofecoxib or celecoxib and this was not broken out in the data that I am going to show you. Importantly, there were no serious adverse events reported in any of these patients.

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If you look at the events, there were no cardiovascular events in either the COX-2 or any of the 530 children that were on other NSAIDs. Five of the 58 had abdominal pain on COX-2; 4 of the 530 on the other NSAID. There were no skin changes in COX-2; 4 on the other NSAID. The two patients in the COX-2 that reported CNS changes, the parents reported changes in mood in one and hyperactivity in another. We didn't have that data broken out for the other NSAID group. Other side effects, such as hematuria, elevated liver function tests, etc., were seen in the other NSAID group and not the COX-2 group.

This committee will have to make its decision regarding celecoxib's use in children based on all the available data. I ask the committee to please keep in mind that children have

practical needs that adults often do not. Children need safe and effective medications that need to have very simple dosing schedules.

Even parents forget and certainly people that don't have children forget. Children are employed. Ninety percent of children are employed. They go to school. When you fill out a form that says, "your employment, what do you do for a living" they say "student." Most schools do not allow children to take medications or have nurses to distribute medications during the day. Therefore, BID and, hopefully even single day dosing, is optimal for children. Children also need palatable medications, something that they can get down easily. You should all recognize that children up to age 12 often do not swallow pills. Therefore, it is critical that it be easily swallowed and also palatable. Children have much more discriminating taste than we do, I think, as adults. Finally, I would like to reiterate that children with arthritis need their physicians to have a larger armamentarium of medications to help

combat their diseases.

I really thank the committee for the work you do. I thank you for giving me this time to present this data to you and I hope it is helpful.

MS. CLIFFORD: Thank you, Dr. Haines. Our last speaker today is Dr. Harry Gewanter.

DR. GEWANTER: Good morning. My name is Dr. Harry Gewanter. I am a pediatrician and a pediatric rheumatologist from Richmond, Virginia. I am here, speaking on behalf of the American Academy of Pediatrics. My statement has been approved by the executive board of the Academy. I have no financial or other relationships with Pfizer or any other companies.

The Academy represents over 60,000 pediatricians whose mission is the attainment of optimal physical, mental and social health and well being for all infants, children, adolescents and young adults. I am a pediatrician and pediatric rheumatologist who is privileged to serve on the executive committee of the American Academy's section on rheumatology.

The Academy does not, and will not, support the approval or denial of any specific medication for use in children. However, on behalf of the children we serve, especially those with juvenile rheumatoid arthritis, or JRA, we do wish to emphasize a number of issues for you to consider in your deliberations.

Children are not small adults. While this is an obvious statement, it is often forgotten in the world of health policy discussions. Children are growing and developing human beings and their response to medications may be significantly different from that of adults. A simple example is the delivery system of all medications that will be administered to children. While issues such as palatability, pill size, etc. are not usually a large consideration in adults, they can be absolutely crucial in determining whether the pediatric patient will actually receive the prescribed drug. The potential risks and benefits of any medication may be different in children and adults, and we urge you to keep this concept in the

forefront throughout your discussions.

Second, as has been stated by many others, there are limited therapeutic options for children with juvenile rheumatoid arthritis. Even with the magnificent recent advances in the treatment of juvenile rheumatoid arthritis, we still have relatively few therapeutic agents available. Further, we know from the over 25 years of pediatric trials and clinical use of non-steroidal anti-inflammatory drugs that s class is generally safe and effective within the pediatric population. We also know that there is a wide range of individual responsiveness within the class. From a practical standpoint, that means we can usually find an effective NSAID for any particular child, but this choice must be individualized. It may take a number of trials before we can find the right NSAID for that child. We believe it important that pediatricians have the option of as many safe and effective NSAIDs as possible so that we may better reduce the pain and inflammation of our patients with juvenile rheumatoid arthritis.

Third, no one can tell the future. This is another obvious statement but it bears repeating. We are gathered here in an attempt to predict the future consequences of today's decisions. No one has that ability and we can only make our best judgments based on the admittedly incomplete data available. Regardless of whether you choose to approve or deny the application today, we need further ongoing monitoring of this and all pediatric medications so that we may improve the care of the children we serve.

On behalf of the American Academy of Pediatrics, I would like to thank you for your time and the opportunity to speak today. We know that you will do your best to improve the lives of the thousands of children with juvenile rheumatoid arthritis. Thank you.

DR. BATHON: I would like to thank all the speakers that we heard from in the last hour for your personal perspectives and for the information that you have provided to us on behalf of yourself or the agency that you represent.

We will now take a lunch break and instead of reconvening at 1:15, we will start sharply back here at one o'clock.

[Whereupon, at 11:50 a.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

Questions from the Committee

DR. BATHON: I would like to proceed with our afternoon session. The first part of the afternoon session will be devoted to questions and comments primarily to clarify any outstanding issues from the morning presentations.

Before we get started, I am going to ask you again to turn off your cell phones and laptops. When you ask a question or make a comment, please identify yourself beforehand. Yes, Dr. Chesney?

DR. CHESNEY: Dr. Chesney. I wondered if I could ask Dr. Lowery for slide number A60 which looks at the systolic blood pressure changes. I wondered if you could just amplify on that a little bit. I am interpreting it as between 6 and 13 percent of the patients developed equal to or greater than a 15 percent increase in systolic blood pressure, which seems fairly significant to me in view of the potential cardiovascular changes with time.

DR. LOWERY: Certainly. I think I will

start by addressing just some methodologic issues within the study. If you recall, the study was started back in 2002, prior to the increased vigilance with regards to, in particular, blood pressure effects of all NSAIDs. I think also in the context that this is a pediatric population, perhaps not the easiest always to take blood pressure measurements, nor was such rigor used as one would use in an adult hypertension study. However, if we could just have slide A60 back on the main screen, just to remind the committee of the data?

So, the mean changes changed a little, with slightly greater effects with naproxen, greater than 15 percent at baseline at any visit. Then the effects worsened. I would also draw your attention to the decreases from baseline, therefore suggesting some variability in the data. So, some patients also had a decrease in the baseline.

I would now just like to bring up a different slide because we have done some post hoc analyses given the greater scrutiny of these data.

If I could bring up B114?

This represents some analyses we have done using recent definitions for diagnosis of hypertension in children. These are the baseline data for systolic blood pressure of patients falling below the 90th percentile based on their age and gender. Showing a baseline pre-hypertension represents the children falling to the 90th and 95th percentile. Stage 1 hypertension represents patients above the 95th percentile plus 5 mmHg and stage 2 hypertension represents patients above the 99th percentile for their age and gender. As you can see, it is consistent with the data I showed on the population level for childhood in general. Around 4 percent of patients in our study did have diagnosable systolic hypertension. If I can now show the slide for the visit data? I believe it is 115.

So, when you look at the changes for the patients over the duration of the study, how did patients change? Did they move from one category to another for the three different groups, low dose

celecoxib, high dose celecoxib and naproxen? Patients who moved from normal to pre-hypertension had slightly lower rates of change for the lower dose celecoxib; similar rates between the high dose and naproxen, from normal to stage 1 hypertension; similar rates between the lower doses of celecoxib and naproxen. No patients in the high dose celecoxib from pre-hypertension to stage 1. Hypertension, only patients in the naproxen.

I would point out that the percentages represent really isolated cases or individual patients. However, together with the mean data, the available data do suggest that some effects are present with both celecoxib and naproxen, as one would expect with this class of agents, but overall the data available to us suggest that these effects are similar.

DR. BATHON: Dr. Davis?

DR. DAVIS: I have a question for Dr. Lowery as well on slide A76 in terms of pharmacokinetics. It stated here that comparable to adults JRA patients require higher

milligram/kilogram doses to achieve similar plasma levels. I was wondering if you could expand upon that a little bit more in terms of the age groups in terms of their metabolism or clearance of the drug, whether that has an effect on it and whether that was looked at in terms of (a) efficacy, (b) safety, and (c) how that is going to relate to the dose that is proposed for the drug.

DR. LOWERY: Certainly. I would like to ask one of my colleagues to come up and present some data on the differences in the doses and responses we saw. Then at the end of that I can show you some other data available for a primary analysis we did by age.

DR. KRISHNASWARMI: Slide C9. Here is a plot of celecoxib clearance observed from study 195 basically plotted as a function of body weight. The triangles represent the adult RA patient data who were also part of this study. The open circles represent the clearance values. As you can see, over the range of body weights in the study clearance increased but much less proportionally

than would be expected. So, if you convert this into a milligram/kilogram scale you can say that the clearance in the smaller weight groups is higher compared to heavier children and adults.

As of now we do not know in terms of the reasons or potential metabolic capacity in terms of increased clearance on a milligram/kilogram basis. However, normally if you look at the raw actual clearance values as a function of weight, you do tend to increase from, you know, lower to higher weights. It is a little bit more steep according to alimentary relationships; it is a little less steeper compared to alimentary.

DR. DAVIS: Did you look at it in terms of age, not just weight, because some of these patients may be obese?

DR. KRISHNASWARMI: Right. Yes, so the effect of age on top of the weight relationship was evaluated in the PK analysis and age was not a significant covariate.

DR. DAVIS: And how about in terms of JRA subtype, systemic, pauci and poly?

DR. KRISHNASWARMI: Clearance as a function of subtypes? There was no adverse evidence of different clearance values for the three groups.

DR. DAVIS: And in terms of efficacy and safety, was there a difference between those that more rapidly cleared the drug?

DR. LOWERY: If we could bring up slide B21? This slide demonstrates the differences in efficacy or the observed efficacy data at week 12, again using the primary analysis, the ACR Pediatric 30 response, for the smaller, lighter children age 2-4, children age 5-7, children age 8-12 and those aged over 13 years of age or over. Indeed, the smaller children gained good efficacy. I would caution in terms of the interpretation with regards to the size of the groups in the study. So, one has to look at the difference in variability with regards to confidence intervals. We are using much smaller sample sizes for these subgroups. But in general efficacy was seen across all age groups, and efficacy was observed in the region of 60 percent up towards around 80 percent in each of the

three treatment groups.

If we move on to this slide which gives a summary of adverse events with the low dose celecoxib group, the high dose celecoxib group and the naproxen group we did see proportionately more adverse events overall in the two younger age groups with celecoxib compared to the naproxen group. So, 60 percent of patients in the lower age group went to 90 percent, 76 percent and respectively in the 5-7 year olds 77, 66 compared to 54.

Overall, as I mentioned earlier, withdrawals were relatively uncommon. We did see three withdrawals in the younger age group with high dose celecoxib; one in the next age bracket and two in the lower dose celecoxib group compared to none in naproxen. As I mentioned earlier, there were five in total serious adverse events, none in the youngest age group; two in the next age group, that of the CMV hepatitis and the asthma case.

We explored these data a little more with regards to these apparent imbalances. So, looking

across here for the younger age group of patients, those aged 2-4, any event, 76, to 93, to 60 percent. However, in general the adverse effects were related to infections that we have seen earlier, respiratory disorders, GI disorders, general disorders, and now we are down to really some small numbers in terms of the number of cases.

Looking at the preferred terms by groups of patients, adverse events, experienced by two or more. Those were cough, pyrexia, abdominal pain and the two liver function abnormalities I referred to in my main presentation, the patients withdrawn from the study.

Looking again at the events causing withdrawal, one case of hypersensitivity and the two liver function test abnormalities I referred to earlier.

Looking at the slightly older age group, 5-7, by system organ class, again, 66, to 77, to 54 percent. So, a slight imbalance, again, general disorders being common and GI disorders.

DR. BATHON: I think that answers the

question. Thank you. I believe Dr. Holmboe had a question.

DR. HOLMBOE: Actually, I have a couple, if I could, or one for the committee. This is mostly for the rheumatologists, given that I have heard that for pauciarticular JRA NSAIDs can be potentially used as a single agent, and given that oftentimes you need to change among NSAIDs in order to deal with toxicity, is it conceivable that NSAIDs, in effect, could be a drug-sparing agent that may prevent them from having to go on to other types of drugs that have been discussed today, much in the sense of the idea of a corticosteroid-sparing agent? I bring this up because, obviously, Celebrex is being used in the field. Whether it has been approved or not, it is pretty clear from what has been presented today that it is out there. So, the question is does anybody have any data to suggest that by being able to switch to yet another NSAID it may prevent kids from having to go on more actually toxic drugs, such as methotrexate, corticosteroids and the

anti-TNF drugs?

DR. BATHON: Would one of our pediatric rheumatologists field that?

DR. O'NEIL: Sure. Kathleen O'Neil. Certainly, one thing that is very apparent from my 25 years in the field is that individuals with even pauciarticular juvenile rheumatoid arthritis will have inter-individual variability in their response to any given non-steroidal anti-inflammatory and that switching a child from drug A to drug B may, indeed, be the magic bullet. I use those terms in quotations.

But there are children who do not do well on two or three different non-steroidals who, when they go to the fourth, now respond. So, the answer is, yes, of course, having more options gives you an opportunity to try something that may be less toxic than the next alternative down the line.

DR. BATHON: Yes, is this in response? No? We will put you down on the list. Was there any other discussion from the pediatric rheumatologists with reference to that point? Dr. Lehman?

DR. LEHMAN: I think the basic concept is that, yes, you can take many of the pauci's and control them with non-steroidal anti-inflammatory drugs, and having a variety available is there. Within that, there are some with more severe disease who are not going to respond. But I think this is going to give a significant percentage of children another option where they may respond and be prevented from using potentially more toxic drugs down the line.

DR. HOLMBOE: Eric Holmboe, I would just like to follow-up. Do we have any data on how often that actually occurs? You know, how often that actually occurs between NSAIDs and how often that switching between classes in this particular condition is successful?

DR. LEHMAN: On an anecdotal basis I can answer that. I have never seen any published data that would suggest that but anecdotally, I mean, in my own practice it is very common to try two or three non-steroidal anti-inflammatory drugs looking for good effect and tolerance before you even

consider moving to a more potentially aggressive drug unless the child obviously has more aggressive disease.

DR. BATHON: Dr. Morris?

DR. MORRIS: I had a question about the design of the efficacy study. The question is about the rationale for the lack of a placebo group. Are placebos ever used in these studies? Is it an ethical issue or is it more of a "we just assume that we know that the drug will work as a companion?" That is more for the FDA people I guess.

DR. SIEGEL: The issue of the optimal design for studies of new agents in JRA is something we would like the committee to consider. I can begin with a couple of comments. A number of different designs are used for studies of JRA.

For the biologics a common design has been a randomized withdrawal study which does involve use of a placebo but in a very special situation. All the children will be enrolled in an open-label study of the new agent and those who respond are

randomized to blindly continue the study medication or go to placebo. Then efficacy is assessed based on whether the children are more likely to flare if they are withdrawn to placebo. That is what was used for the approval of Enbrel and it has been used in a number of other situations as well.

In some situations a placebo control induction design has been used but that is very unusual. It was used for the infliximab study but there were specific reasons for that. I think pediatricians don't like to use that design because it involves giving a placebo injection in some cases to children who are in pain, and IRBs are reluctant to approve that sort of design. Even if it is not an injection, giving a placebo to a child who has active disease is problematic if there are approved medications that are available. So, that is a problematic design.

But there are other ways that it could be done. In our adult RA trials we often allow early escape. Once a patient has been proven not to respond to the medication after a certain number of

weeks they are declared a non-responder for purposes of the primary endpoint, and then they are allowed to get the drug open-label. So, this is something that we are thinking about a lot, about the best design.

DR. MORRIS: Well, I was asking about study 195. Obviously, when you reviewed the design it was decided that no placebo was needed and I just want to understand the logic behind that at that time.

DR. MEYER: This is Dr. Meyer. One of the things I want to stress is that I think our sophistication with non-inferiority trials has changed over time but, you know, as opposed to the situation that Dr. Siegel was just talking about where you are talking about a controller drug and you can still be using symptomatic treatment for pain on top of it, what we are talking about here is if you want to do a true placebo trial and you don't want it heavily confounded by the use of rescue medicines you would get into very a difficult situation because the kids are having

pain.

So, while I don't think it is impossible to think of designs that would be placebo-controlled, I think it is much better, considering that you are talking about pain and symptomatic relief in kids who are symptomatic, to use a positive control design. That said, it gives you the difficulty of defining your non-inferiority margin.

DR. MORRIS: Yes, I guess my understanding is that either there are ethical reasons or there are design issues where you think you know that the comparator drug will work and I just wanted to get a sense. What I am hearing is that it is kind of more the ethical problems.

DR. MEYER: I think it is more on that side than it is full confidence in the non-inferiority margin. As Dr. Siegel said in his presentation, I don't think we have full confidence in that.

DR. BATHON: Dr. Daum?

DR. DAUM: Thanks. I have a number of questions but I will ask them sort of one at a

time. Dr. Lovell presented three slides, numbers 3, 4 and 5, that go to understanding the disease burden that we are talking about today that whatever therapy is prescribed or imposed has to deal with. My concern is that the data are 20 years old on those three slides. It is from the mid-1980s. I have heard this morning from rheumatology colleagues that the therapy has changed and they manage the children much better now. But are these really the outcomes still, that more than 60 percent of children have articular erosions and more than 60 percent don't play sports, or is there an update from the last 20 years? I guess that is my question.

DR. BATHON: Dr. Lovell, do you want to answer that?

DR. LOVELL: So, can we bring up those slides? What I said in my comments was that I hope the erosive disease is actually better now than it was back then. But the studies we have that look at x-ray damage are actually all older studies. We have some difficulty now doing radiologic studies

because of radiation exposure. I would suggest that this data is probably still pertinent and that a large number of our patients still do have pain. Would you go to the next slide?

Actually, what I said here was not that 60 percent of the kids don't play sports; it is 60 percent of the kids have pain that interferes with their ability to play sports. Actually, a lot of the kids are very stoic and they will play sports, and they will play soccer even though they have to limp around and that sort of thing or they have intermittent pain. But it is not to say that 60 percent don't participate in sports. I think that actually a far greater number do participate in sports. It is just that in this data it said that 60 percent of the time kids have pain that interferes.

DR. DAUM: Well, I am happy to say it your way but my question is, is the number 60 or 65 percent still correct?

DR. LOVELL: I would probably say it is less.

DR. BATHON: Do we have data or another opinion? Dr. Lehman?

DR. LEHMAN: Data is hard to come by for this kind of a study with radiation, etc. Clearly, the clinical experience is that since the introduction of the tumor necrosis blocking agents those children who don't do well on non-steroidal drugs get a dramatically improved response with those. So, the number of patients we have with inhibition and functional impact is dramatically reduced. Whether the adult data in the reduction in erosions is transferrable to children has not been shown.

DR. DAUM: Do you have any sense of the articular erosion update? I mean, I understand the radiology issue that has been raised but, again, these data are 20 years old also.

DR. LEHMAN: My personal belief based only on my own private practice experience would be that erosions are dramatically reduced by the use of the anti-TNF agents as well. I am not prepared to prove that statement.

DR. BATHON: Let's move on to the question. Dr. Weise is next on the list.

DR. WEISE: This question relates to the available formulation. Unfortunately, I didn't write down who gave this information so somebody can chime in, but there was a slide that showed that a group of patients, 10-25 kg, were receiving 50 mg BID. This is a huge range of actual dose delivered to patients. If you figure that that is 100 mg a day in a 10 kg child, that is 10/kg; in the 25 kg child that is 4/kg. And, it looked as if there was a trend on the adverse event data towards more adverse events with the higher dose ranges. So, I wonder if someone from Pfizer could address whether a formulation that would allow us to target more closely a particular dose range is possible through sprinkles being measured out carefully, or would there be more different sizes of drugs that could be offered to increase safety?

DR. BATHON: Somebody from Pfizer? Thank you.

DR. KRISHNASWARMI: I would just like to go