back to the plot that shows the relationship between body weight and clearance. The point here is that it is relatively flat. Much of the variability in the data, although there is a statistically significant covariate, is not explained. Given the flat relationship, what we came up with was shown in a schematic in C25.

The overall approach is as follows: We collected data from over 95 percent of the patients in the trial so we had two doses, 3 mg/kg and 6 mg/kg. What is shown here is the steady state PK profile for a certain patient of a certain weight. So, these are the two profiles. The overall approach that we took with the capsule dosing regimen is to achieve concentrations in between the two doses for every single weight group across the spectrum of weights observed in the trial.

For example, here is the profile of a capsule, PK profile for a certain given weight that is achieving concentrations in between those. So, what we did was we repeated this exercise across the weight spectrum and tried to see if we could

come up with capsule doses that would produce concentrations in between those of the two doses. So, that is why we came up with the 50 mg dose for 10-25 kg patients and 100 mg dose for patients weighing over 25.

I would like to go into more data if you would like to see every weight group in terms of the projected concentrations for the capsule.

DR. WEISE: Well, I am not sure if that would be helpful, but do we have anything that tells us whether 10/kg, which the smaller kids on that dose would receive, is safe?

DR. LOWERY: Bring up B32. It is a very similar representation. I just showed you the adverse event data by age. These are, likewise, data by body weight. Keep in mind that the lightest children, and there are only several children, three in the low dose group and one in the high dose group and none in the naproxen group are reporting any adverse event at any stage of the study. This is the heavier group, between 13-25 kg, shown here across the two treatment groups.

There is a slight imbalance in terms of the higher dose celecoxib compared to naproxen but, likewise, an imbalance with naproxen for the other dose groups. In terms of withdrawals, no patients withdrew in the lower dose group; one and four in the next weight category. Serious adverse events only occurred about the 9-12 kg group. So, our data are limited realistically in these lower dose groups. There is no clear pattern of a different toxicity profile compared to the other weight groups.

DR. BATHON: Although from one of your prior slides it did seem that the younger kids had more toxicity. Is there a chance that they are getting a higher dose? I am confused by why age doesn't correlate better in terms of adverse events.

DR. LOWERY: Yes, the younger kids did have overall more adverse events but when we broke them down they were more sort of adverse events that one would expect in this age group, although from the exposure data proportionately the younger, lighter

kids got less exposure to the drug than the heavier children because the are clearing it on a weight basis more efficiently than the older children so they are getting less exposure to the drug.

DR. BATHON: Dr. Sandborg, I have other questions. Is this relating to the matter-Bno? Then we will proceed with Dr. Proschan's question.

DR. PROSCHAN: Yes, at first glance it looks like on some of the secondary outcomes the 3 mg dose is not as good, for example, you know, slide A43 seems to show that. But it looks like that is explained by the baseline differences and I am just wondering-BI don't know if you have A43 to put up.

Yes, so at the bottom left corner it talks about p less than 0.05 for one of the comparisons. But I am wondering, it looks like that would go away if you adjusted for baseline differences so I am wondering if you did that and if it did go away. I mean, it looks like that p value might be comparing a given time point rather than a change from baseline or any other way. Is that correct?

DR. LOWERY: The p value is comparing the doses at the given time point. But perhaps to understand these data a little better because of the differences in the baseline mean, I would just like to bring up the mean change from baseline because of the differences in baseline. It might be a bit more interpretable for you.

DR. PROSCHAN: Right, that is really what I wanted to see.

DR. LOWERY: Yes, just bring up the slide. There were some differences in the baseline means, if you recall, so with the lower dose celecoxib there was some efficacy still demonstrated at the week 2 treatment, different to the higher dose, as demonstrated in the previous slide. And, naproxen falls in between the two dose groups.

DR. BATHON: Does that answer your question?

DR. PROSCHAN: Yes. Can I just ask one other?

DR. BATHON: If it is quick.

DR. PROSCHAN: Okay. One of the slides,

and I am not sure which one it was, had abdominal pain and then it had upper abdominal pain, and the upper abdominal pain was greater than the total abdominal pain. I am wondering what happened there.

DR. BATHON: Maybe while you are looking for that slide we could go on to the next question and come back.

DR. LOWERY: It is probably relatively straightforward to address because there are different preferred terms as compared to the system organ class. So, a patient could be counted in abdominal pain and abdominal pain upper and both of those adverse events were reported but they would score only once for the organ class.

DR. PROSCHAN: Okay. I also noticed in the briefing document that there was headache and then there was also sinus headache. I was wondering does the headache category include all of them or not the sinus ones?

DR. LOWERY: Headache and sinus headache would be preferred terms. If a patient reported a

headache and a sinus headache he would show up in both categories but only once under the nervous system disorders.

DR. BATHON: Thank you. Dr. Holmboe, you had a question?

DR. HOLMBOE: Yes, I have two questions for Pfizer. The first is that I wanted to know why you picked an inferiority margin of 25 percent. While I understand that it has implications for the sample size, I am a little concerned by the 25 percent because since the outcome measure was a clinical scale looking at function and pain, a 25 percent difference on that scale, to me, would seem to be clinically and functionally significant. I think you got away with it but I would like to know what your rationale was behind choosing what appears to me, from a clinical point of view, a fairly wide margin.

The second thing is that in your plan for ongoing monitoring you mentioned that you plan to follow spontaneous reports. However, we know those aren't very good for picking up safety concerns

and, clearly, efficacy studies are very limited in addressing safety concerns. I think we saw that today; we saw that two years ago; I think we are always going to see that.

To me, this seems to argue very loudly for a registry. You have a disease that is somewhat rare but not infrequent. You know, you have thousands of these kids so it is not like you are dealing with a small database. You can create a registry that I think could be very powerful and really answer some of the long-term questions that I think are on the minds of everybody. Although there is no evidence that NSAIDs accelerate atherosclerosis, we do have concerns that as they enter later age they may develop atherosclerotic disease and because of their underlying inflammatory condition they are going to get into trouble, and without a registry we are not going to know that. Spontaneous reports are going to be a very weak instrument to do that. So, I wonder if you would address those two things.

DR. LOWERY: Certainly. If I could address

the first point with regards to the non-inferiority margin, as I presented, it was deemed to be appropriate at the time both in terms of what would be a clinically meaningful difference and what was agreed to amongst advisors on the design of the study and with the agency. I hope that I showed you that subsequently the efficacy we did see in the study would have justified a more conservative efficacy margin of even 15 or 13 percent. Had we chosen 10 percent it would have been a study in excess of 1,800 patients and simply undoable in this population.

With regard to spontaneous monitoring--

DR. BATHON: Could I interrupt you? I am sorry, but Dr. Proschan wanted to comment on the choice of the 25 percent also. Then we will come back to the registry.

DR. PROSCHAN: Yes, I think it is true that 25 percent is too big. I think the FDA probably shouldn't have agreed to that, if they did. But it is really a moot point at this point because, you know, the only thing that is important now is that

confidence interval which shows that it is better than that. It is only, at most, 13 percent worse. So, what the margin was--you know, whether it was set too high or not--is really irrelevant at this point. The only question is what does the confidence interval show? How much different are they? How much worse is Celbrex, if any?

DR. BATHON: Thank you. The registry issue?

DR. LOWERY: Pfizer has a great deal of experience in looking at various pharmacovigilance issues, and I guess one way to frame the question is what is the safety concern we are looking for. If the safety concern is rare effects that we did not see in this efficacy trial or very, very rare effects in this population such as treatment-related cardiovascular outcomes, there we have a good degree of confidence in spontaneous reporting. We are already addressing, albeit in the adult population, how to delineate what the cardiovascular risk is for selective inhibition of COX-2 versus non-selective inhibition of COX-2.

Although this is in a different population, we feel this is the best way to translate certain long-term effects with regards to cardiovascular safety.

With regards to what are the very long sequelae of treatment in childhood, we have considered such methodology such as registries and, as I think as one of the panelists commented earlier, even a registry in that setting is going to be impaired by the ability to follow sufficient numbers of patients for sufficient time to explore any potential impact on risk. Hence, that is the basis for our current proposal.

DR. BATHON: And I think we can have more discussion on this during the issue of safety and what further studies we might recommend as a committee. Dr. Boulware, you had a question?

DR. BOULWARE: Actually, Dr. Holmboe had asked the question I was going to so I withdraw it.

DR. BATHON: Dr. Sandborg, you are next.

DR. SANDBORG: A question again about the non-inferiority margin. I guess this is for both Dr. Lovell and Dr. Siegel in looking at placebo

rates, we have very little experience with this endpoint, the definition of improvement and the placebo-controlled trials. So, the only one I believe that we have is the infliximab trial which, in and of itself, is very different because that is an IV intervention and, therefore, the placebo rate, given that, may be unusually high because of the intensity of the intervention. There are some older studies that use a blended scale, and I am going to ask this to Dr. Lovell, in methotrexate and placebo, and other things where the placebo rate is something less than 25 percent, how do those endpoints relate to this or that placebo effect relate to this?

DR. LOVELL: We did do older trials in which we actually had longitudinal placebo. As you say, that preceded the ACR Pediatric 30. But we utilized that data when we were developing the various definitions. We had that data in a standardized database and that was the exact data we used to develop the ACR Pediatric 30 definition. So, with a little bit of maneuvering we could

actually calculate placebo response rates in those earlier trials using the ACR Pediatric 30.

What happened was that we see placebo response rates for d-penicillamine, hydroxychloroquine and methotrextate that are in the range of 20-30 percent. These were patients with polyarticular disease who were on placebo therapy for anywhere from 6-12 months. So, the patient population was slightly different but the placebo response rates used in an approximation to the ACR Pediatric 30 definition were in the range of 20-30 percent.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: I wanted to come back to the issue of a relationship, if there is one, between the chronic use of NSAIDs and blood pressure since one of the issues I think we are concerned about is long-term cardiovascular risk. I wondered if any of the rheumatologists could tell us if there have been any long-term studies of systolic blood pressure in children on chronic NSAID use compared to normal children. I just picked this up and I

may be totally out to lunch but I just need to be reassured that there is no issue between chronic NSAID use and blood pressure changes.

DR. O'NEIL: I am unaware of any formal studies to that effect. This is Kathleen O'Neil, for the people who can't see me. But, certainly, in monitoring these children at every visit they get blood pressure checks. The experience in my 25 years of pushing pills is that the children who have hypertension generally have it unrelated to whether they are on non-steroidals or not but, rather, more related to such issues as familial history of hypertension, obesity, inactivity, etc.

DR. BATHON: Dr. Proschan, did you have another question?

DR. PROSCHAN: If I did I sure don't remember it!

DR. BATHON: It flew out of your mind? Dr. Daum is next.

DR. DAUM: I have two questions that go to dosing. The first one is, is it well established that the blood levels you alluded to several times

are correlated with effect and efficacy? Then, the second question is if you could say maybe a sentence or two about what the problems in bringing a more kid-friendly suspension or preparation would be.

DR. KRISHNASWARMI: This is a little bit of a busy plot here. I would just like to walk you through it. What is shown here is the relationship between the administered exact milligram doses and the relationship to efficacy response as a function of time. There are four panels here. Each panel is for a certain time point. The Y axis is the responders and the X axis is the milligram dose that is administered. So, what you see here is the line that indicates the slope based on a logistic regression analysis and it shows the relationship between dose and response. This is actually the individual milligram doses that each patient received.

As you can see here, it takes a little bit of time for the lower doses to show the response but at later time points, especially week 8 and

week 12, it appears that the drug reaches pharmacodynamic steady state. Over the range of doses between the individual doses that are administered the responses vary anywhere between 60 and about 80 percent.

If we look at the same plot as a function of the blood levels, which is in the next slide, C51, a similar relationship emerges. Here you have the AUC on the X axis and the same efficacy response on the Y axis again showing the dose response that is more obvious at early time points than at later time points. You can achieve similar responses. Does that address the question?

I would like to turn it over to Dr. Schumacher for addressing the formulation question.

DR. SCHUMACHER: I think Dr. Lowery had already explained that we had some issues specifically with developing the dosage forms. I am going to point out the last several bullets here related to the suspension.

We had difficulties in scaling up--and this is a multi-year development effort--and

specifically matching the performance properties of the suspension that was used in the clinical trial. From a clinical scale going to a commercial scale manufacturing process, we could not match those properties. In lieu of pursuing that further, we opted for the sprinkle capsule approach. This particular capsule formulation is ideally suited for that because there is no specific taste with the contents of the capsule.

I don't know if you want me to go through the other dosage forms but your question was specifically about the suspension.

DR. DAUM: I just wonder, I guess, if it is a solvable problem. I mean, it doesn't look like you want to say much about what the problem was, and that is okay, but suspensions are so much more kid-friendly that I am just wondering whether the problems can be solved for the future perhaps.

DR. SCHUMACHER: Sure. Could we go to slide C64, please? The issue was in particular associated with aggregates and we have scanning electron micrographs of the properties of material

that was used in studies to evaluate the suspension. What we could not do is match the properties of the clinical lot, shown above in the upper left, without extensive manipulation of the manufacturing processes, and this was a significant effort in terms of the equipment and the capability of the equipment. That is representative of the particular case of what we underwent to try and do this. Does that help explain it?

DR. BATHON: Dr. Morris?

DR. MORRIS: Yes, I had a couple of questions relating to spontaneous reporting. In the briefing material that you sent you have an analysis of cases reported in children less than 16 years old and I didn't see any cardiovascular effects at all in that report. So, are you saying that from your spontaneous database you see actually no cardiovascular effects reported in children less than 16? I am assuming that is true.

DR. LOWERY: I believe we reported from the original data set that there was one deep vein thrombosis. Subsequent to the cutoff data for the

initial sNDA and the four-month safety updates through our research, and particularly through the survey that was presented a little earlier, we identified one case of pulmonary embolism in the patient who was reported to have--

DR. DAUM: But there is none in the spontaneous reporting?

DR. LOWERY: There are no cases of myocardial infarction or stroke reported to us--

DR. DAUM: Well, you don't have any cardiovascular events listed. It is Table 14.

DR. LOWERY: Sorry, that report is all organ classes. In the wording you will see the deep vein thrombosis reported and also comments on the pulmonary embolism case.

DR. DAUM: I am sorry, I couldn't understand what you said.

DR. LOWERY: I said in the text around the table you will read regarding the deep vein thrombosis and the pulmonary embolism case.

DR. MORRIS: Maybe you can show me later. The other question I had was that in the

presentation that you made you talked about enhanced spontaneous reporting. I think that is the term you used in the slide. I didn't understand what that meant and I wonder if you could describe that.

DR. LOWERY: Certainly. So, with any sort of large-scale marketed product a great deal of spontaneous adverse events are reported and what is important is to identify if you have a specific pharmacoviligance or safety concern, say, for example severe cutaneous adverse reactions or cardiovascular events in childhood in anyone under the age of 18, to ensure that we gather the maximum amount of information and to focus targeted efforts. So, when those reports are initially phoned in the initial documentation triggers a series of questions and we put in a lot of effort to ensure that we capture any concomitant medications, etc.

DR. MORRIS: So, it is not enhancing the reporting; it is enhancing the data collection--

DR. LOWERY: The data collection.

DR. MORRIS: One other question, do you have a slide that might show the cardiovascular events reported for adults during the same time period?

DR. LOWERY: Not on hand.

DR. MORRIS: But do you know if we have any cardiovascular--

DR. LOWERY: I don't, but I think the adult cardiovascular reporting rates are a good example in some regard of how identification of serious events with spontaneous reporting works better than identifying small changes in common events. So, to give the example of non-steroidals being on the market for 20, 30 years and risk of those events failed to be picked up, however, with other events and other drugs they are picked up.

DR. MORRIS: I would have expected a lot of flooding but I also would have expected more from the pediatrics, if there was anything, so that is why I was surprised.

DR. LOWERY: Overall, we definitely saw an increase in overall safety reporting in 2004, 2005.

DR. BATHON: Dr. Siegel wants to address this point.

DR. SIEGEL: I wanted to go back to the issue of the dose-response relationship. I think the members of the committee were asking about the wide variability in dose in milligrams/kilogram that children would get and how that might affect efficacy and safety. The two slides that the sponsor showed didn't exactly address that. You showed milligrams versus response, which doesn't correct for the weight, and you showed concentration versus response, and physicians don't target a serum concentration. But there is variability in the milligrams/kilogram children receive because of the same dose for a range of weights. So, do you have that same plot where you put milligrams/kilogram on the Y axis, where you plot milligrams/kilogram versus efficacy?

DR. KRISHNASWARMI: No, we don't have that plot on the milligram/kilogram scale.

DR. BATHON: Dr. Proschan, is your comment a question related to the cardiovascular issue?

DR. PROSCHAN: Yes, Table 14. Table 14 does say with reporting rate greater than 2 percent. So, presumably if it is under 2 percent it wouldn't be in this table, which kind of bothered me a little bit. Also, the fact that, you know, it looked like as soon as they went off the drug any adverse effect would not be counted, and I am wondering if that is correct or whether, you know, once they went beyond a certain time point they wouldn't be counted.

DR. BATHON: I think we need clarity on whether there were any cardiovascular events other than apparently one pulmonary embolus, and is this the same pulmonary embolus that was reported in the observational internet data that we heard about?

DR. LOWERY: Sure. There were two events, both venous thromboembolism, one a deep venous thrombosis reported I believe in a 14-year old following surgery, and one case of PE reported in a 16-year old with psoriatic arthritis.

DR. BATHON: And no MIs?

DR. LOWERY: No MIs.

DR. BATHON: Does that answer everybody's questions? Dr. Gorman?

DR. GORMAN: To follow-up on Dr. Chesney's question about blood pressure because now I can't let it go either, this drug does change renal blood flow. Is that true or not true? I know it changes absorption of fluid through the loops of Henle because it says so in the label so it must be true. Does it change renal blood flow and is that a potential cause of hypertension or increased blood pressure in these patients?

DR. LOWERY: So, in normal, healthy adults I don't have the data to hand, but there are some effects and transient effects on sodium retention with selective COX-2 inhibitors in general and celecoxib specifically, but no effect in healthy kidneys on renal blood flow.

These were the baseline means estimated using the creatinine, actually, towards the high end as one would expect in childhood; the mean change from baseline, really little change across the groups. We did an assessment of patients who

came close to 100 and no patients did. So, in this population we didn't see any dramatic effects on renal function with this analysis.

DR. BATHON: Dr. Davis?

DR. DAVIS: In terms of slide A38 looking at the pediatric DOI 30, is this slide observed data? Is this an intention-to-treat analysis? If you have that on another slide broken down, observed, intention-to-treat or non-responder?

While you are looking for that, the second question is did you look at baseline factors that were predictive of response getting to the issue of generalizability of the study to the overall pediatric population with JRA?

DR. LOWERY: The data on intent-to-treatB-I am sorry, I didn't catch the second part of the question.

DR. DAVIS: The second is did you look at baseline predictors for response in the patients?

DR. LOWERY: We looked at subgroup analyses for pauciarticular, polyarticular, systemic, DMARD use, corticosteroid use in general--I showed a

couple of them and the response rates were similar across treatment groups. We can go into those in detail if you want to see them.

DR. BATHON: Did you want any more clarification on the ITT? Is it less observation carried forward?

DR. LOWERY: Sorry. Yes, it was.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: Forgive me that I keep coming back to this because I don't use these drugs routinely so it is an unknown to me. But in the package insert for Celebrex, under hypertension it says as with all NSAIDs, Celebrex can lead to the onset of new hypertension or worsening of preexisting hypertension either of which may contribute to the increased incidence of cardiovascular events. Then it goes on to say that patients taking thiazides or loop diuretics may have an impaired response and so on, and so on.

So, apparently this is a known complication and, again coming back to children who tolerate a lot of things better than adults do, I

am just wondering if it isn't an issue as to whether we should look at the long-term blood pressure of children on NSAIDs again, looking to see if they are at higher risk when they become adults for cardiovascular events. I don't know if some of the adult rheumatologists could comment maybe on your patients with chronic NSAIDs. Is there any reason to think that they become more hypertensive or hypertensive faster compared to controls? I am not phrasing that very well.

DR. BATHON: Dr. Boulware or Dr. Davis, would you like to respond and then if Pfizer would like to respond to this as well?

DR. BOULWARE: In terms of adult patients for all of the NSAIDs we use, the risk factor of their hypertension worsening or tipping them over into a hypertensive phase exists, and it is something I watch carefully for them. So, it is a recognized risk for me.

DR. DAVIS: Yes, I routinely have patients come back for follow-up blood pressure as well as serum creatinine.

DR. CHESNEY: Does it relate to duration of NSAID use or is there reason to believe that some people are idiosyncratic for this? Is this predictable?

DR. DAVIS: This is only anecdotal but I worry, particularly when I am changing the dose or when I am initiating the dose.

DR. BATHON: Dr. Siegel, do you want to speak to this in terms of the database for NSAIDs in adults? Do you have any comment? Or Dr. Rappaport? No? Dr. Boulware?

DR. BOULWARE: Let me just add that the risk is bad enough that I won't even use it in someone who has renal insufficiency or borderline renal insufficiency because of that likelihood of them going into renal failure and that is all NSAIDs.

DR. BATHON: Does the sponsor want to comment at all?

DR. LOWERY: I think just the comment that some risk for hypertension is evident for all agents that inhibit prostaglandin, and that is

common to selective and non-selective agents.

DR. BATHON: Right, a class effect for sure. Dr. Weise?

DR. WEISE: This question relates to reporting of adverse events and any possible relationship to the physicians that are taking care of kids with JRA. It was mentioned that only a third to a half of these patients are cared for by pediatric rheumatologists. This question I guess is to our pediatric rheumatologists. Do you have any concerns about the likelihood of non-rheumatologists being well attuned to the potential risks and be likely enough to report those? Maybe Pfizer would have some information on who has been reporting most of the adverse events in kids.

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: I do think this is a concern in general in the field when we have not enough pediatric rheumatologists and there are quite a few children being cared for by non-pediatric rheumatologists who appear to be mainly adult

rheumatologists, who do get some training in pediatric rheumatology, and then elsewhere pediatricians usually. This is a concern because they tend to use more NSAIDs and don't move on to the more disease-modifying agents perhaps as quickly. So, I think it is a possibility that more of that population of children would get exposed to these types of NSAIDs.

DR. BATHON: I don't have anybody on the list and our hour is just about out. I wonder if I could just ask a question myself to our pediatric rheumatologists? That is, one of the compelling reasons to develop COX-2s for adults was the problem of GI bleeding from non-selective NSAIDs. We are hearing that GI hemorrhage from ulcers in children is extremely rare. So, the compelling reason for COX-2 development for that reason would be less compelling in kids. So, my question is in the pediatric rheumatology group is there enough abdominal pain that is not well enough treated by conventional NSAIDs and PPIs or H-2 blockers that justifies or compels us to move towards the COX-2

drugs? Dr. O'Neil?

DR. O'NEIL: I think the answer to that is yes. I think all of us know that although we don't have gross GI bleeding as commonly as is seen in adults, perhaps because they don't smoke and drink and abuse their guts for as long, nevertheless, the children have substantial abdominal pain, falloff in appetite and irritability related to that. Growth failure is not uncommonly seen and a drop off on weight for height in children who have non-steroidal anti-inflammatory drug-induced gastritis, perhaps without overt bleeding. These children sometimes do respond to the addition of an H-2 blocker or a PPI. But then we are talking about exposing a child to two different classes of drugs with their concomitant side effects, as well as the expense, and the difficulty of multiple drugs, multiple doses, multiple yuckies in a small child which often will wind up on the clothes of the child rather than in the child.

DR. BATHON: Are there any data comparing a COX-2 drug with a conventional NSAID plus a PPI for

safety or efficacy in kids? There aren't any in adults, I don't think. Are there any other questions or comments or clarifications?

DR. TURK: Can you hear me?

DR. BATHON: Yes, Dr. Turk?

DR. TURK: It is a bit odd for me to be coming in an out and, hopefully, I haven't missed much. Just a question about perhaps efficacy and maybe the design of the study. When I looked at slide A45 it appeared that the levels of pain that Dr. Lowery presented were in the neighborhood of below the moderate level or no advance on the BAS scale. I also understand that the majority of children who have JRA will have had a trial of naproxen. Is that correct?

DR. BATHON: Could you repeat that question one more time?

DR. TURK: Are the majority of children who have JRA started on naproxen?

DR. BATHON: Are the majority of children with JRA started on naproxen? That is what we heard, yes.

DR. TURK: Therefore, when we look at these data at baseline the children who are randomized to the naproxen group are basically children who have failed naproxen?

DR. BATHON: Can the sponsor answer that?

DR. LOWERY: As an inclusion into the trial you did not need to be failing your current NSAID treatment.

DR. TURK: Right, but these individuals are children who, at all the baseline levels, reach a certain level that warrants them to be included in this trial and I am assuming that they are being included because they are not well treated on their existing medication.

DR. LOWERY: Not necessarily. Any patient with a baseline mean above 11 mm whilst on treatment with their existing treatment and who were deemed to be eligible for ongoing chronic NSAID therapy were eligible for inclusion into the trial. Patients were taken off their baseline NSAID for a period approximating five half-lives of that drug and then randomized to treatment with

either celecoxib or naproxen doses.

DR. TURK: But the baseline mean scores that were seen in A45, are those after they had been taken off of the naproxen?

DR. LOWERY: Yes, indeed, that is correct. That is the baseline pain score, not the screening pain score which would have been taken some days before.

DR. TURK: Then one other question, you nicely showed the responder rates on the JRA 30 and I wonder if you have data on the responder rates on pain, a parent's assessment of a child's pain looking at a 30 percent responder and a 50 percent responder to the three different drugs.

DR. LOWERY: I don't have that with me.

DR. TURK: So, we don't really know what percentage of the children achieved what that is sometimes referred to as a clinically meaningful change on the pain?

DR. LOWERY: You are correct. On pain alone we have not calculated that. We could calculate it relatively easily. But I would

perhaps draw your attention back to the global assessments where 80 percent of patients responded 30 percent or greater on physician global assessment of disease or parent's global assessment of disease.

DR. TURK: I understand that but I still would like to see the data on the pain rating separated out from that because I think pain doesn't necessarily get reflected as well as we would like in that type of measure.

DR. BATHON: Maybe I am not hearing correctly but wasn't your slide 45 pain response?

DR. LOWERY: We have mean improvement.

DR. BATHON: Oh, just mean?

DR. LOWERY: Not the percentage that responded by 30 or 40 percent.

DR. BATHON: It is not a standard outcome though, is it, 30 percent response in pain per se?

DR. RAPPAPORT: It is in pain trials.

DR. BATHON: It is? Not in arthritis I guess. Dr. Boulware?

DR. BOULWARE: I was reminded of the

question I had. Were all of the patients who entered this study on an NSAID before entering the study and then went through the washout, and how many of them were on celecoxib, if any?

DR. LOWERY: I can answer the question. I know no patients were on celecoxib. If we could bring up 599? So, approximately 60 percent of patients across the different treatment groups were receiving NSAID prior to the study, about half of those were naproxen and diclofenac, ibuprofen, some rofecoxib, etc.

DR. BATHON: We can take one last question. Dr. Daum?

DR. DAUM: This is a question of curiosity more than anything else. As I understood the presentation this morning, the trial was ongoing when Vioxx was withdrawn from the market. My question is what did you do in terms of patient information when that happened? Secondly, what kinds of reactions did you get from parents of children who were about to enroll or were already enrolled?

DR. LOWERY: So, I believe we were pretty much around the time of all patients entering into the open-label phase of the study during those events. A process of re-consenting took place for all subjects in the study to inform them of the new information. As regards individual anecdotal reports I don't have anything to add.

DR. BATHON: Thank you. We are going to take a short break now and reconvene for a discussion at 2:20.

[Brief recess]

Questions to the AAC and AAC Discussion

DR. BATHON: What the next part of our afternoon will be spent on is some discussion and then voting. What I would like to do first is deal with our first discussion point about need for new therapies and then move directly onto the two questions regarding efficacy and safety, discuss each of those in depth and then take a vote at the end of each of those questions. So, we will discuss first need for new therapies, then move to our questions. Yes?

MR. LEVIN: This is just a point of information. I mean, I would wonder whether we talk about Celebrex as a new therapy. It is an existing therapy. It is simply not an approved indication but it is not like we are discussing, when we are discussing Celebrex, a new therapy.

DR. BATHON: I guess it is semantics in a sense but it will be new approved therapy if it were approved by the FDA.

Our first discussion point is to discuss the need for new therapies in children with juvenile rheumatoid arthritis, including therapies such as celecoxib. I think just to start this off some of the issues that were raised, in particular during the public session as well as the discussion by the committee, were things like having more options; having access to drugs that FDA approval would afford; having a drug with a different mechanism of action for perioperative management; having different dosing capabilities and different routes of administration and palatability. So, those are some of the issues relating to the drug

armamentarium that had come up during the discussion. So, do we have any comments or discussion on this? Yes, Ms. Dokken?

MS. DOKKEN: This is broader than the question but I really feel the need to put it on the table related to the question about new therapies. I am impressed-BI was going to say troubled, but impressed by hearing that the largest percentage of children with JRA are not treated by specialists. Hearing the specialists who are here talking about treatment, it brings back that term about medicine being an art and not a science. It is in that context that it sounds like at least some people are saying new therapies are needed.

And, the parents who spoke in the public meeting clearly were parents who were informed, had really been on top of their children's chronic illness and I think they alluded to a very good relationship with that kind of specialist. It is sort of troubling to not be able to put that context around our discussion because it, per se, isn't what the FDA does but I think it appears to

be a huge part of the issue.

DR. BATHON: Any comments on that? We did hear in the background data also that the majority of the prescribers of Celebrex are actually orthopedists for ankle sprains rather than JRA, interestingly. Could we hear from the pediatric rheumatologists about your opinions regarding the need for new therapies, using "new" in the context that Mr. Levin pointed out?

DR. SANDBORG: I think that although this is not a new medication, it is challenging to understand how to dose and apply for this medication to insurance companies, and like that. So, I feel that the need to have more choice for these children would be very valuable so I think there is a need for these types of medicines to be considered.

DR. BATHON: Dr. O'Neil?

DR. O'NEIL: I think that the data presented by Dr. Yancey and also the overview by the Pfizer representative, Dr. Lovell, discussing outcome in juvenile arthritis shows that even

though we may be improving our treatment outcomes, (a) we haven't documented that 100 percent yet because the treatments are changing even as we speak and, (b) there is still a very big gap between an optimally functioning young adult at the end of having juvenile arthritis for 10 or 20 years and what we actually are producing currently.

There are a number of issues related to treating children that define which drug we use in clinical practice. It was alluded to but I think I can't emphasize how big of a stumbling block it can be to have to try to dose a child three or four times a day with a medicine that may not taste good, or may just be a power play and reinforce the issues of dependency and the problems of lack of independence from parent; the consequent enmeshment that can occur; the psychosocial issues, and so forth, aside from just trying to get it into them in school, and that remains a big issue. So, yes, there are populations of children that need something that can be given once or twice a day.

The other issue is that there are children

who will respond to drug A or drug B but not C, and vice versa, in a very as yet unpredictable manner. So, having the availability of more than three drugs in a class that we can use for children is important.

The other issue with respect to having a need for drugs is that, in addition to trying to treat inflammation, we are also trying to treat the pain issue. Although when the inflammation is gone the pain is often much better if not, indeed, gone, if there is substantial damage it may not be gone because if the cartilage has been destroyed there is still going to be substantial pain, and these long-acting anti-inflammatory medications remain an important part of their treatment. I think the young lady who spoke about her upcoming hip surgery spoke to that directly.

The bleeding issue, certainly, surrounding surgery makes drugs of a COX-2 inhibition class attractive in certain defined settings where they may not even be necessary if someone doesn't have a major surgical procedure coming up because they may

be somebody who absolutely tolerates the classical non-selective NSAIDs.

So, there are a lot of issues and I think that variability in what we can choose to individualize treatment for a particular child is an important issue that we can't overstate; shouldn't understate.

DR. LEHMAN: If I can just add a couple of things to that, I think it is important for those who deal with adults and not with children to recognize that medication compliance is probably one of the most difficult issues in pediatric rheumatology. It ranges from parents and physicians who are unwilling to give a drug that hasn't been officially FDA approved to children who see medication as a form of power over their parents, just like green beans, Brussel sprouts or broccoli and will often refuse to eat what they are being told to eat. Green beans, Brussel sprouts and broccoli I might take their side with, but they need the pills for their disease.

So, it is important to realize that we

have very limited things that actually come in liquid form. The more liquid medications we have or medications that come as sprinkles, which is what this is being proposed as at this point that can be easily put into applesauce or something like that for small children, actually becomes a major issue because they can't swallow pills and they do object to taste.

You know, it may seem ridiculous to say that all NSAIDs are not created equal in this audience, but I have seen a number of patients over the years where somebody put them on Naprosyn and when they failed Naprosyn said, okay, NSAIDs don't work for you; you need methotrexate. We need to have a large body of well-established drugs that can be used as an alternative because we have all seen children who were on Naprosyn who didn't respond, who did respond to another non-steroidal anti-inflammatory drug and, indeed, never did need methotrexate.

There needs to be much more thought and much more available medication that we can use in

order to prevent people from making that one-step jump or, okay, there is nothing else that comes in a liquid and you don't like the taste of pills-Bjump. We need the advantages that an additional formulation will give you, if it is opening capsules, and we need the advantages of having a different medication which is different from both Naprosyn and is a selective COX-2 inhibitor for at least the potential benefits on bleeding, bruising and hoped for decreased GI toxicity.

DR. BATHON: As a point of clarification, can we assume then that the sprinkle formulation is as patient-friendly as the suspension or nearly so, or not? I got that implication from what you were saying.

DR. O'NEIL: If we had both, that gives you that much more option. It sounds like at the moment a suspension is not an option and a sprinkle does add a different possibility to the treatment.

DR. BATHON: Would you encourage the sponsor to continue to try to work on a suspension?

Is that what I am hearing, that you would prefer a suspension but a sprinkle is a pretty good second choice?

DR. O'NEIL: From the perspective of the very small child where dosing on a per kilo basis is only by gross estimate by increments of 50 mg or 100 mg, I think it probably makes a big difference. The very small child often won't take the granules in their applesauce or just won't take the applesauce.

DR. BATHON: Dr. Gorman?

DR. GORMAN: There is an alternative which is that the USP could publish data that says what the appropriate formulation for a crushed pill or a crushed sprinkles could be, which would then have the same regulatoryB-I am not a lawyer and I never played one on TV, but I think they have a similar regulatory effect as an FDA approved formulation.

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: I think either sprinkles or liquid are very good. The problem with the sprinkles in this case is, again, that the dosing

intervals are so great that you are going to have some patients treated at 10/kg and others treated at a very low dose. So, I think that either would be acceptable. One consideration could be that you make the increments smaller.

DR. BATHON: Dr. McLeskey?

DR. MCLESKEY: I was just going to make a comment to be supportive of the sponsor on the issue of new formulations. It may or may not be obvious to some of the clinicians in the room; it certainly was not obvious to me when I was a clinician but I have learned since moving to industry that you can create new formulations, and obviously the sponsor wants to make the formulations that are most user-friendly or patient-friendly and would be the most readily accepted in the marketplace, especially in this pediatric population, but I have learned through some hard knocks myself that you create a formulation in the laboratory and it is just extremely difficult to scale it up to a commercially viable product. It is doable but

frequently it costs so much in research and production costs that then, once the product is made, it is not accepted in the marketplace. So, I have empathy with the sponsor. I am sure they will work on new formulations but there is difficulty there that is universal in the industry.

DR. BATHON: Yes, Mr. Levin?

MR. LEVIN: I just want to clarify something. Given the fact that several surveys that we heard about today indicate that at least among specialists in treating JRA Celebrex is already out there being used, I just want to make sure I understand that the most important benefit, outside of the insurance issue which I don't think is on the table in this meeting, is the dosage formulation. The drug is already being used by a vast majority of specialists so approving the new indication or not approving the indication, children treated by specialists for JRA are getting the medication. Am I right that the most important benefit, therefore, to moving it as a new indication is to have a dosage form which increases

compliance and, therefore, hopefully will increase the beneficial effect of the drug?

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: I think that because a lot of people are using it, that based on just that alone we don't need to approve this-BI think that is actually probably incorrect. I think that understanding the safety and the increased pharmacovigilance that approving such a drug might bring would actually allow both families and certain physicians to feel more comfortable using it in understanding that there was monitoring, and such, going on.

MR. LEVIN: Could I just clarify what I said? I agree with you but we haven't heard that shoe drop yet in the conversation. I agree there is good reason, besides the dosage formulation, to make this a new indication but I haven't heard discussion of the kind of safety surveillance that would go along with that that would convince me we are on the right track in terms of safety oversight here.

DR. BATHON: Yes, we are going to talk about safety in a few minutes. Is there any other discussion on this question of the need for new therapies? Do adult rheumatologists or any of the drug safety folks want to comment?

[No response]

So, we heard that there is some need for new drugs to treat kids with juvenile rheumatoid arthritis. In particular, we need drugs that increase the dosing flexibility in the NSAID class; that insurance coverage might be easier if it is approved; that it would be beneficial in terms of perioperative management; that compliance might be enhanced for both children and parents because of the formulation, the easier BID dosing and the fact that it might be FDA approved and that parents might like it more. One of the other advantages is that by increasing the available drugs in the armamentarium it may enable postponement of DMARDs in pauciarticular disease, and it adds to the different formulations that we have in terms of this sprinkle formulation. Any other additions to

that or comments to that? Yes, Dr. Morris?

DR. MORRIS: Just one addition, and that is I can understand where pediatricians or specialists who treat this disease are willing to use an off-label drug. I guess my thinking is it is more the generalists who might feel, because it is now approvedB-I think the data that FDA offered in briefing showed that there was a big downturn in the number of prescriptions for this product, and will this approval add to an upturn among generalists. So, it might be a willingness to prescribe issue for generalists. Even though a lot is used, I get the sense it is more the specialists that are using it.

DR. BATHON: May I ask the FDA is it appropriate for us to have a discussion of what we think the scenario would be like if the FDA were to approve the drug? For example, what you say may be true and there would be a lot more advertising so would there be a lot more usage of the drug for lesser indications like sprains and minor injuries, and be prescribed by a much wider group of

pediatricians? Is that something that we should be discussing?

DR. MEYER: Well, you are certainly free to discuss it. From a regulatory standpoint, we pay the most attention for the approval decision to the data on the indication and the labeling for that indication. That said, from a safety perspective we do also have to pay attention to how the drug is used when it is approved. But, again, from the FDA standpoint in terms of the approval decision, we are most focused on the indication in question.

DR. BATHON: Yes, the way I would put that question is, is it better to approve a drug with perhaps an unclear benefit/risk ratio or low unregulated use in which there is no monitoring? So, on the one hand, if it is approved there can be monitoring. If it is not approved there wouldn't be monitoring but there may be exaggerated use for lesser indications. Somebody had a comment. Dr. Gorman?

DR. GORMAN: Could someone from the agency comment on advertising restrictions for drugs with

black box warnings?

DR. MEYER: The only main restriction is for advertisements that are called reminder ads where it doesn't have complete information. So, there is no other absolute restriction on advertising. Specifically, although there has been some discussion about limitation of direct-to-consumer advertising with these kind of drugs, just backing to the general question about black box warnings or boxed warning, there is sort of a general perception that boxed warning drugs cannot be done as direct-to-consumer advertising and that is actually not true. They can be. It is just that fair balance insists that as a part of that advertising they make the information in the box very clear.

DR. BATHON: Dr. Morris?

DR. MORRIS: Just to add to what Bob was saying, there is kind of this informal policy that information that is contained in the black box appear in the fair balance statement. There was a letter sent out just this month, I think it was for

Seroquil, that was a complaint that said that new information in the black box was not included in the fair balance and the FDA took action against it.

DR. BATHON: Any other discussion on this point?

[No response]

So, we have laid out some needs for new therapies and some of the downsides of approval versus non-approval. What I think we should do then is to move on to the first question on efficacy. So, do the available data demonstrate that Celebrex is effective in the treatment of juvenile rheumatoid arthritis? If not, what additional studies would you recommend to further assess efficacy?

If I could just start this discussion, we heard some discussion in the previous hour that 25 percent non-inferiority margin might be too large but, nonetheless, the 95 percent confidence interval was well below that. We heard also that the placebo rate may have been underestimated

because of the recent Remicade trial which showed a placebo rate of 48 percent. But we also heard that the placebo rate for older studies, when retrospectively analyzed by ACR P 30 criteria, were in fact lower than that 48 percent. So, maybe we could have a discussion about efficacy based on these numbers and the data that we saw. Dr. Holmboe?

DR. HOLMBOE: I am a little uncomfortable with the way the question is framed. It says do the available data demonstrate Celebrex is effective. I haven't seen anything today that speaks to the effectiveness of this drug. Effectiveness relates to how this drug performs out in the environment, in the marketplace. All we have seen is a non-inferiority trial to this point. So, I think it is important to keep that in mind. We are looking at a limited amount of data on efficacy. We have no data on effectiveness.

DR. MEYER: Can I just make a clarification? The actual Food, Drug and Cosmetic Act refers to effectiveness. The split of efficacy

versus effectiveness that has become sort of popular in outcomes research, and so on, occurred well after the way the Food, Drug and Cosmetic Act was worded and voted in.

DR. HOLMBOE: I think that is really important because I think some people reading this will make a distinction between these two terms so I appreciate the clarification.

DR. BATHON: You would accept the word efficacy?

DR. HOLMBOE: Yes.

DR. BATHON: Dr. Proschan, do you want to comment from a statistical point of view?

DR. PROSCHAN: Yes. I mean, from a statistical point of view, again, you know, there has been discussion about the design and non-inferiority but if you believe that placebo is going to be 13 percent worse than naproxen then I think you have to grant that celecoxib is better than placebo. I think, you know, by and large the evidence suggests that it is effective.

Actually though, a point that Turk raised

on the phone was actually interesting that I hadn't really thought about. You know, who is going to get into this trial? It is the people who are not happy with the way their disease is going. They are not being helped that much. And, if they are all starting on naproxen, then that does raise an issue that I hadn't thought of that, you know, these are basically people who were on naproxen and were not happy with the way things were going and those are the people that are in largely. I think that is worthy of some thought. I think that is not to be dismissed.

To me, when I look at all the evidence it suggests that overall it is effective but there are certain issues like the one that Turk raised that are worthy of consideration I think.

DR. BATHON: I guess we don't know the motivation for people coming into the trial exactly. It is an assumption that you are making to some extent. Dr. O'Neil?

DR. O'NEIL: I think that with pediatric rheumatology drug trials these days we are very

able to recruit families and children, because you need both, where there has been a good effect with the initial drug but they believe that we need other therapies. They believe that it is worth testing other therapies and they are willing to be a part of the study to help forward the science. I think that a lot of that depends on the community of physicians bringing the drug to trial and actually affecting the trial. But I think that at least in the small number of trials I have been involved with because I believed that there was good equipoise in the trial, I had no trouble convincing people who lived close enough, or whatever the rate limiting step may have been, to participate in a trial even if they were fairly well controlled on their initial drug.

DR. BATHON: Dr. Daum?

DR. DAUM: Could I ask for a clarification because I now end up a little bit confused? Were the people who were invited to participate in this trial all folks who had been receiving naproxen before? From the inclusion criteria and exclusion

criteria in the sponsor's presentation I can't quite get that. I felt that when Dr. Turk said we said, no, that wasn't right.

DR. BATHON: Could the sponsor clarify that for us? DR. LOWERY: About 60 percent of patients at screening were taking an NSAID. In total, about half of those were on naproxen. So, in total only about 30 percent of patients coming into the study were on naproxen ahead of the study; 40 percent were receiving no NSAID.

DR. DAUM: You didn't have to be failing or doing poorly to get in. They were just on it. Right?

DR. BATHON: Right. After the washout or not being on it they had to meet certain clinical activity criteria.

DR. DAUM: Right, but that is an important point. So, they weren't necessarily failing or were naproxen failures. I think it is crucial that we understand that.

DR. PROSCHAN: Right, but still the point is that if you are doing really well on naproxen

you are probably not going to want to get into the trial. I mean, it is not a hard and fast rule. I am saying there might be a tendency in that direction.

DR. BATHON: Yes. Dr. Sandborg?

DR. SANDBORG: So, in looking at the baseline characteristics, although it was fairly-BI don't want to say easy but this was really designed for milder arthritis with just needing one swollen joint. Almost half the patients were on methotrexate and the average early joint count was I think-Bcorrect me, somewhere between four and six active joints, which suggests that patients had ongoing active disease even in spite of methotrexate and NSAIDs. So, I would say that these were not necessarily patients who were unhappy with NSAIDs because of them actually needed more than NSAIDs. They just had active disease and the question is if they needed an NSAID, you know, what would be the best that would help improve that disease activity.

DR. BATHON: Dr. Gorman, I think I missed

you.

DR. GORMAN: Dr. Sandborg just made my point much more elegantly than I was going to.

DR. BATHON: I think the design is fairly similar to adult NSAID trials in terms of a washout and having to have some activity. It is a washout with a flare or persistence of disease activity. Is that fair to say? Any other comments? Dr. Davis?

DR. DAVIS: I just wanted to point out too that if we do accept that this therapy is effective in the treatment, we thinkB-or I think it is effective in the short term. I just wanted to clarify that too. And, if we do think that this drug is effective or we vote on it as being effective, I just wanted to say it is effective, given the data that we have in 2006 with a very short-term study.

DR. BATHON: Right, so the clarification is we can speak to efficacy only up till 24 weeks, and more appropriately in the first 12 when we had some comparator group. Mr. Levin?

MR. LEVIN: Does that speak to the indication on the label? I mean, if we make that amendment, in a sense, to the question and our vote, that would then be the indication? Or, would the advice to the FDA be that the indication be for short-term treatment?

DR. BATHON: So, when we vote on efficacy are we limiting our vote to short-term efficacy or should we be generically saying efficacy for any duration of treatment?

DR. RAPPAPORT: The study, as designed, was to look at chronic use in this patient population.

DR. BATHON: Chronic pain but for a short duration study. Dr. Siegel?

DR. SIEGEL: It is probably worth mentioning that for studies of diseases looking for chronic use the typical duration of the study is three months unless there is a reason that the study needs to be longer. For example, in multiple sclerosis it is typically longer. In lupus it is typically longer because the disease waxes and wanes. But for diseases that don't three months is

a typical duration for a trial for a chronic disease for efficacy.

DR. BATHON: Any other comments or discussion? Is everyone ready to vote then on this point of efficacy? Only the voting members can vote. That means we start with Dr. Boulware on this side and we will go around through Dr. Sandborg. When you vote please state your name first and then the "yes" or "no" answer. The question is do the available data demonstrate that Celebrex isB-can we say efficacious in the treatment of JRA?

DR. BOULWARE: Dennis Boulware, yes, the data do demonstrate that it is effective for the time period that was studied.

DR. DAVIS: John Davis, yes.

DR. O'NEIL: Kathleen O'Neil, yes.

DR. LEHMAN: Tom Lehman, yes.

DR. CHESNEY: Joan Chesney, yes.

DR. BATHON: Joan Bathon, yes.

DR. HOLMBOE: Eric Holmboe, yes.

DR. MORRIS: Lou Morris, yes.

DR. WEISE: Kathryn Weise, yes.

MR. LEVIN: Arthur Levin, yes.

MS. DOKKEN: Deborah Dokken, yes.

DR. PROSCHAN: Mike Proschan, yes.

DR. DAUM: Can I tag something on my vote or do you just want "yes" or "no?"

DR. BATHON: I guess if it is short we can consider that.

DR. DAUM: No, it is very short. I was impressed with the comment of how long this trial went on so my answer is yes, but I don't think we know anything past 24 weeks.

DR. GORMAN: Rich Gorman, yes.

DR. SANDBORG: Christy Sandborg, yes.

DR. TURK: Dennis Turk, yes.

DR. BATHON: Did you say yes, Dr. Turk, or no?

DR. TURK: I did.

DR. BATHON: Yes?

DR. TURK: Yes.

DR. BATHON: I still couldn't understand you, I am sorry.

DR. TURK: Yes.

DR. BATHON: That was a yes. Okay.

DR. TURK: Yes, it was.

DR. BATHON: I think I finally heard it. Thank you. So, it was a unanimous "yes."

The question that follows is if we said no what additional studies would you recommend? So, technically we should not address that question since we voted yes. Dr. Morris?

DR. MORRIS: Does our vote now mean that we are suggesting that the drug meets the regulatory standard for efficacy? Because it is one study and we hadn't talked about corroborating data or anything like that so I wasn't sure what our vote meant.

DR. RAPPAPORT: No, it doesn't. That is a determination we make based on a number of different issues, and agreements, and discussions.

DR. BATHON: All right, well our second question is on safety. Do the available data demonstrate that Celebrex is safe in the treatment of JRA? If not, what additional studies should be

undertaken to further study safety? If yes, do you recommend any phase 4 studies to further characterize the safety?

So, I would like to have a general discussion on safety at this point and then we can come back to these specific sub-questions. Dr. Proschan?

DR. PROSCHAN: When you talk about safety, I am wondering is that compared to something like naproxen or compared to placebo? I mean, it may very well be less safe than placebo but just as safe as naproxen which is being used all the time. So, what is the relevant comparison?

DR. BATHON: Yes?

DR. MEYER: Actually, if you look at the second discussion points now getting folded into this, there we do ask you to put it in the perspective of the alternative therapies, which would mean other NSAIDs as well as other drugs that might be used in this setting.

DR. BATHON: Mr. Levin?

MR. LEVIN: This is where the other shoe

comes in that I referred to earlier. I would be less than honest if I didn't say I was somewhat disappointed with what the sponsor is proposing as safety oversight for a drug with at least a troubled recent history. As clarified by the questions asked by Lou Morris, it did not involve a more robust solicitation of spontaneous reports but, rather, spoke to the analysis of the reports that are received. While spontaneous reporting may be useful in identifying very rare or rare events, we all know and live with the fact that there is tremendous under-reporting. So, number one, I am somewhat disappointed that the sponsor, again given the circumstances, hasn't suggested a plan to have more robust and accurate spontaneous reporting as perhaps one way for addressing the problem.

In talking about what the reasons are for making this a new indication rather than allowing it to just go forth as unapproved use in treating children with JRA, it seems to me that, from a policy perspective, bringing it into the fold should mean that we will mean more about a drug and

a condition that we know very little about. We are making decisions here on very little evidence. It makes me uneasy but I think we are probably making the right decision. But it seems to me that the quid pro quo for this should be the opportunity to learn a lot more and understand a lot more about this drug and this population for this use. You don't do that, it seems to me, in the sponsor's plan which is simply a more detailed analysis of those spontaneous reports that come in.

I think we need to talk about the registry notion again. I think we need to really consider that in return for making this an indication, as a society we need to get something in return and that something should be advancing our understanding of both treatment of the disease and the particular benefits and risks of this drug.

DR. BATHON: Dr. Holmboe?

DR. HOLMBOE: Actually, I was going to cover most of what Arthur just did so I would just reinforce his points, particularly around the issues of the registry and long-term tracking. I

think that we need more than just spontaneous reports for all the reasons Arthur laid out.

DR. BATHON: Dr. Weise?

DR. WEISE: I am also concerned that we don't have safety data beyond the short term of the study, especially because these are children who will be using or experiencing this drug through a long childhood and into adult age. The specific question asked is has it shown safety. My read of it is yes, for now. But I do agree that there should be a societal responsibility. Whether that includes government, industry and physicians taking care of these kids, or some combination of these, I think the long-term follow-up has to be done.

DR. BATHON: Dr. Boulware?

DR. BOULWARE: I support all of this too and I just want to add a little more reason for pushing this registry issue. We do have data that obesity has hit this country like--whatever--right now. I mean, it is just a wildfire. With that we have seen the incidence of diabetes go up I children and is skyrocketing. I think Alabama is

even number one or number two in the country now. It is not something we are proud of.

We don't have data yet but there will be a follow-up of cardiovascular disease as diabetes goes up and it will be very hard to sort out which is causing what and a registry would actually help tremendously to sort out if it is the obesity and the diabetes or the use of the drug on a long-term basis in a child for an extended period of time, which will show up earlier or later when they are in my clinic.

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: I think that the pediatric rheumatology community would endorse the idea and the need for long-term registries, not just for this medication but for all of the newer medications and for the old medications such as naproxen. We really have no mechanism to do this and there is a great deal of interest in the community to partner with our adult rheumatologists when we do pass these kids on as they become adults to see what the true risks are in this population.

DR. BATHON: Dr. O'Neil?

DR. O'NEIL: Our greatest concern I think as we look at the toxicity profile of this class of drugs is the potential for adverse cardiovascular and thromboembolic events. It is helpful to think about what the rate of thromboembolic events in ostensibly healthy children or children as all-comers is. Data by Maureen Andrew out of Toronto sick kids who ran a registry for thromboembolic events in childhood in Canada, published a few years ago, shows that the incidence rate in children is 7/million/year. When we are talking about trying to define a risk ratio in a population where it isn't even known what the baseline risk is in the kids with chronic inflammation, it is going to be very hard to tellB-you know, if we get to 14/million/year that is a doubling of the risk ratio; 21/million/year is a tripling.

So, the answer is we may never see it so it may not be an issue. But there may be a very substantial increase in risk that I think is going

to be difficult to get at but important to understand. The one analogy I can think of is the use of aspirin and its link to Reye's syndrome. Reye's syndrome is an extraordinarily rare event, and even more so since aspirin was found to have an epidemiologic link, but it wasn't until three million children were surveyed and their use of medications looked at that one was able to identify that there was a tripling in risk if aspirin were used concomitantly during a febrile illness. So, it may be a long time before we have a definitive answer to a 7/million/year rate amplification to who knows what.

DR. BATHON: Dr. Gorman?

DR. GORMAN: I have concerns about the registry. It sounds like a great idea. I don't think it should sit inside of any pharmaceutical company for a bunch of obvious reasons, obvious to me at least. And, the concept of following a disease as complex as juvenile rheumatoid arthritis with multiple subclasses and rapidly evolving therapies and then just tracking people who take

one drug for one specific period of time, and then potentially blaming all potential outcomes on that one exposure sounds to me to be really not the right focus.

I would think that a registry would probably have to sit inside the National Institutes of Health and look at the disease as a process rather than as the drug therapy because the questions you were asking before about if you don't know the baseline rate, it is really hard to tell if you have increased the risk and it becomes a real issue. The concept of a simply registry might not give you any information at all and might give you bad information, at worst.

DR. BATHON: Dr. Proschan?

DR. PROSCHAN: I was just going to comment on how much information you can really get when you have no events out of 100, say. Really the only thing you can be pretty confident about--you know, if you do a confidence interval, then you can be pretty confident that the true rate, if you had enough people, would be no more than about three

over N where N is the number of people. So, if you have a hundred people and nobody has the event, nobody has a CVD event, then you can be confident only that the true event rate is probably no greater than about three out of a hundred, which is not telling you very much when you know that in kids it is not going to be anywhere near that anyway unless the drug were really bad.

So, I just want to support the idea that really we don't have much information about safety and we certainly don't have information about the long-term safety. Of course, that is what is of real concern, you know, the idea that it might cause an MI when they are 30. The only way to try and address that is to follow people long term.

DR. BATHON: Yes?

DR. HOLMBOE: A few more points about registries, I mean, I think we are thinking of them far too narrowly. Registries are very helpful to track chronic disease and if you look at what has been done in some other adult chronic diseases what we have learned from them has been very powerful.

It is not just the safety issues. There is also quality of use on medications. One of our concerns is that these drugs will not be used appropriately, either dosing concerns or that they are not being used by certain folks in the right, I guess, use.

But I would encourage people to think beyond just the narrow safety and looking for rare events. Registries are much more powerful in looking at disease across conditions. I was struck in listening to the pediatric rheumatologists about the variability in treatment. Why is that? Is that really the best thing to do for these kids, particularly given the number of drugs that are being used? So, I would encourage us that, you know, we ought to think in broader terms, recognizing that this shouldn't necessary fall on the pharmaceuticals as well.

DR. BATHON: Dr. Sandborg?

DR. SANDBORG: I would just like to make one more follow-up to the registry concept. I think as the pediatric rheumatology community talks about registries they look at the large concept of

registry and the value that you would get from looking across diseases, multiple medications, natural history, usage, standardization of care, in addition to safety and outcomes. So, I think that it would not be helpful to follow these 200 children, or however many there were, forever because that will simply never have the power to identify these rare events. We really need to have a very wide-ranging, very large effort to be able to pick these things up.

DR. BATHON: So, it sounds like there is a fair amount of enthusiasm for suggesting a registry, but not just limited to celecoxib but to all NSAIDs if that were possible. That is not necessarily going to be possible for the sponsor to do but through perhaps another mechanism as well, like NIH sponsored trials. And, it is not just a short-term registry but we really need in this situation perhaps 10 or 20 years of follow-up, which is extremely challenging, especially from an NIH funding perspective. So, these are difficult issues.

If I remember right from FDA rules and regulations, you can suggest a registry; you can't require it or tie it to your approval or disapproval decision. Is that not correct?

DR. MEYER: It depends on how you use the word "require". But they commonly are made part of phase 4 commitments or risk minimization plansB-not commonly but it is not unheard of. Those are commitments from the sponsor that I think in our experience have generally be adhered to. So, in the very strictest sense they are voluntary on the part of the sponsors but they are often included, in certain circumstances, with approvals.

DR. BATHON: Are there other studies that people think should be done, other than suggesting a registry of some type? Are there specific cardiovascular studies that you think need to be done? Are there risk factor assessments in a registry or some other interventional or observational study that needs to be done? Does anybody think that there are any GI safety studies that need to be addressed? You can think about

that for a second. Dr. Lehman?

DR. LEHMAN: I just want to make everybody aware that we need to be very careful in that all of us recognize the need for much greater amount of information about the long-term outcome of children with rheumatic disease and, indeed, the long-term outcome of children and adults with a wide variety of conditions. But I don't think we can tie that to this Celebrex in any meaningful way, and I think we need to keep those two issues separate from each other.

DR. BATHON: Dr. Morris?

DR. MORRIS: I would agree. I think your point about we shouldn't try to do everything within a registry makes a lot of sense, you know, to try to follow people forever. I would opt for a more limited set of questions, more short term, looking perhaps at surrogate markers in terms of blood pressure rises and things like that.

I don't know whether case-control studies are feasible even now. It seems that there are people put on this drug already and there may be

kids who have been on it for a number of years but I don't know whether that would show up in an insurance database. I don't know whether it is feasible or not. But I would suggest that over the long term looking it, some of the long-term issues in a case-control study makes a lot of sense, and limiting the registry for more short-term questions I think is the way to go.

DR. BATHON: Dr. Boulware?

DR. BOULWARE: Perhaps another surrogate we could do is imaging studies that are done over a shorter period of time on some of these patients who have been on the medication for 24 or even 48 weeks or, hopefully, even longer than that. I don't know if they will show a change that would happen in that patient population but perhaps imaging studies, the more sophisticated ones that are coming out.

DR. BATHON: Subclinical cardiovascular evaluations?

DR. BOULWARE: Right, because in the past what we saw was that it was the non-fatal MIs that

were the real relative risks that were very high in the other adult populations so focusing in perhaps on the coronary artery changes that could occur.

DR. BATHON: Does anybody want to comment on that? Dr. Sandborg?

DR. SANDBORG: I think that we don't know the answer to this. We do know that the blood pressure is a class effect with NSAIDs, that it goes up and we need to be very careful about that. But there are some new imaging techniques such as the endothelial reactivity, the brachial artery reactivity that is a relatively short-term change that might be worth looking at in a population of patients, maybe both adults and kids, to see if there were differences there. Some of the other non-invasive imaging techniques, such as IMT, are still long term, two, three, four, five years and we really don't know what happens in kids with those. But it is possible there could be some surrogate markers for some of these issues.

DR. BATHON: Mr. Levin, is your comment on this issue?

MR. LEVIN: It is more in general to moving away from sort of the registry approach to these other discussions. I think they all fall under the umbrella of what I was trying to say earlier, that the current proposal by the sponsor for increased safety surveillance falls short in my mind. Maybe the message here is that the sponsor needs to work with FDA and others to figure out how to improve upon that. I am not the expert here that can comment on what kind of study, but I can comment that from a public policy perspective there needs to be something more than more robust investigation of the spontaneous reports that come in, from my perspective, to deal with the safety concerns here. However folks who design these studies choose to do it, that is not my area of expertise but I think the message I would like to send is that we absolutely have to link a new indication approval to a more robust safety surveillance program, worked out between the agency, the sponsor and whoever else.

DR. DAUM: Particularly with the emphasis

on long-term safety because the data are what they are and they are 24 weeks long. Maybe not perfect 24 weeks but 24 weeks, but we need to know about long term and I am not sure we are going to be able to sit here and design the right study but I think the message to the agency is that we need to know that. If there is an approval granted, something needs to be in place to try and gather those data once it is started to be used more freely.

DR. BATHON: Dr. Meyer?

DR. MEYER: Not wanting to argue one way or the other on this point, and in many ways I agree with some of the things just being said, I did want to point out that many of the alternative therapies, primarily the NSAIDs, actually have no long-term data in any setting. At least with this drug we have some long-term data, albeit sort of mixed in its message, in the adults.

One thing, on slide A89, and I am not sure it got much notice when the sponsor went through that slide, but there is an ongoing familial polyposis trial in adolescents using Celebrex. So,

this would be a different patient population. They wouldn't have the same kind of pro-inflammatory risk of a JRA type patient but this will be a long-term trial because it is looking at the risk of polyp development in these children, and would provide some additional long-term data in addition to the PRECISION trial which is trying to sort out more definitively in adults whether the cardiovascular risk with Celebrex is appreciably different from either naproxen and/or Motrin.

DR. BATHON: I certainly got a feel that there was a lot of agreement that a registry is very, very important, at least for the sponsor to limit it to Celbrex, obviously. Other registries are beyond the recommendations of this committee I think, even though we all believe that a broader registry is important. Am I correct in assuming that there is fairly general support for this idea of a registry for Celebrex by the sponsor for long-term monitoring? Dr. Proschan?

DR. PROSCHAN: Also, in addition, people were talking about some more sophisticated tests to

pick up signs of cardiovascular problems, I would say probably renal as well because there is some hint that there is a potential problem there as well.

DR. BATHON: If I could interject a comment myself for a second because I study cardiovascular disease in adult RA, one of the problems with the subclinical tests is that inflammation causes a derangement of endothelial reactivity and things like pulse wave velocity. They are abnormal presumably because of inflammation and treating the inflammation actually makes it better. Now we are saying could there be a test where you then reverse it back in the other direction, and that we be really, really tricky I think in this situation. So, I am not sure that these tests are going to be very helpful in chronic inflammation. Yes, Dr. Daum?

DR. DAUM: To respond to Dr. Meyer's comment, I am not sure that the argument that there is not long-term data for other NSAIDs is the one that should carry the day. It is a new era now and

the public is more sensitized to the toxicity of these agents and one has been withdrawn from the market. So, I think if there is going to be a new indication granted people are going to reasonably expect that something is in place to know what the toxicity is of this long term. So, I am not comforted by that.

The second thing is that the ongoing trial that you mentioned is welcome and I think should be maximized and exploited to study the long-term safety issue that we are talking about. But I think what we really are saying here as a group is that we would like to know something about long-term safety in JRA. I am not quite smart enough to come up with a study design sitting here but I think that something has to be in place.

DR. MEYER: I hear that and I wasn't trying to be dismissive of that. I was trying to just point out some of the things that are in place and trying to point out the lay of the land. If the alternative to using Celebrex is using naproxen or Motrin and you don't know what the long-term safety

of those is you may not be in a better place. But I am not arguing with you.

I guess the question in my mind in taking this advice forward is if the registry idea is an advantageous one or a good one, and I am not arguing that it is not, should it be based on a single sponsor or is it possible to get that kind of thing done by some other organization that can look more broadly.

DR. BATHON: Dr. Gorman?

DR. GORMAN: If we are going to create a registry for this agent, then I would suggest to the committee as well as to the agency that it look specifically, or most specifically and actively at the people in that registry for the side effect we are most worried about, which is cardiovascular. I think I have heard from the pediatric rheumatologists during the course of the day that they don't see very many cardiovascular events with their present use of NSAIDs. So, if that should start to appear in the specific one it would give us a strong safety signal.

DR. BATHON: Ms. Dokken?

MS. DOKKEN: Yes, before we get to a vote I guess Dr. Daum just mentioned public awareness, and particularly when FDA meetings take place in a hotel you know that there is a lot of public interest and, as I say, before we vote, I mean, I am uncomfortable with the wording of the question, do the available data demonstrate that Celebrex is safe? I know the word "available" is the key word but I would be much more comfortable if we somehow could amend, you know, available albeit limited. I do think of the sort of responsibility to the public and I want to make sure that it doesn't just come out of this meeting that the committee said that Celebrex was safe, but that there were, you know, reservations around what data our recommendation would be made on.

DR. BATHON: Well, I think the word safe, if I am interpreting this correctly, includes both short- and long-term safety, and what we are hearing is that a lot of people are uncomfortable about the absence of long-term safety data. So, I

think that you could vote. If you don't feel that there is adequate long-term safety data then you would consider voting no to this, that the available data are not indicating safety. Is that correct? Dr. Boulware?

DR. BOULWARE: At the risk of complicating it even more, the question does confuse me in terms of risk and safety. They are really relative questions and relative to what? This question confuses me because I am not sure I know how to answer this, safe compared to what? No treatment or the other available NSAIDs that are currently used for this? So, if I could get some regulatory clarification.

DR. BATHON: We were asked to compare it to other treatments for JRA, to think about it in terms of that, not placebo. Is that correct?

DR. RAPPAPORT: Yes, you were asked to look at this in the environment that it exists in, so including available treatments, other products and the use of unapproved products where you don't know a lot about what your risks are.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: I appreciate all these comments. I guess I also wonder if we can make any statement about the safety of this drug in the long term. I think that all the approvals that went before Vioxx had limited data like this and we thought it was safe, and it wasn't, until we got a whole lot more information.

So, I think I would concur with what you are saying, safe compared to what? Safe compared to other small studies like this of similar drugs? But we really don't know anything about the safety of this drug in the long term for children.

DR. BATHON: Other comments? Dr. Proschan brought up the idea of renal disease. Are there any additional studies that we would recommend in terms of safety? We heard about blood pressure--

DR. CHESNEY: Yes, blood pressure. I feel like I am pounding a dead horse, or whatever the idiom is, but I really would like to see some very careful ongoing studies done in conjunction with nephrologists to look at the issue of blood

pressure in children treated with NSAIDs, and going on into the adult population since we know this is a demonstrated side effect in adults and we know it has to be having similar effects on children. It is just that they are more subtle at this stage, but we may be creating something very new for our adult colleagues 10 or 15 years down the road. I think if we at least had a heads up on it we would be ahead of the game.

DR. BATHON: Other discussion?

[No response]

What I am hearing is a strong recommendation for a registry and as much as we can, if the drug is approved by the FDA, to tie the approval to a mandatory or pseudo-mandatory registry. Preferably the registry would be very long term, as much as can be accomplished. It would focus on all aspects of safety including GI, renal, hypertension, all the risk factors for cardiovascular disease and cardiovascular events themselves.

In terms of other studies, we didn't have

any specifics but we are interested in blood pressure and cardiovascular. Nobody mentioned GI.

We acknowledge that there is no long-term safety data and that is the reason for the registry in particular. We acknowledged also that there is a need for a broader registry under other funding mechanisms that would look at all NSAIDs, selective and non-selective, and this is particularly important in today's climate where there is increasing obesity, hypertension, diabetes in younger and younger folks upon which chronic inflammation may add increased risk. We didn't mention prednisone but that is certainly another additional risk that these kids are susceptible to. Is there any further discussion? Dr. Morris?

DR. MORRIS: I reacted strongly to the word "mandatory" in terms of registry. For lots of reasons, I think that is not a good idea. I would like to give FDA a lot more latitude in the precise type of post-marketing surveillance done. I think it may be a combination of studies. Whether it is a mandatory or limited registry, I would like them

the option on working on something that is feasible. I mean, if this drug is to be used-Bif you are saying a mandatory registry, to me, that says a child could not get the drug unless they are in a registry and that just hasn't worked with other drugs.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: I was going to raise the same issue. Does anybody have examples of registries such as we have been talking about that have worked, that have made a difference, that have given good long-term information? Who is going to pay for this? Who is going to organize this? I mean, rheumatologists will execute it but they are not going to do it free of charge so how realistic is a registry? Do people have other examples of registries that worked well?

DR. BATHON: Dr. O'Neil?

DR. O'NEIL: One example in the pediatric rheumatology community is the TNF inhibitor registry in Germany, run by Garret Tordneff [?]. That has been operant for six or seven years now I

think and has produced some very interesting data supporting both the safety and the efficacy of these drugs, but also identifying other issues that are important.

DR. BATHON: Dr. Siegel?

DR. SIEGEL: We have some experience with mechanisms to get data on long-term exposure to some of the treatments for rheumatic disease. A lot of this comes from the biologics where etanercept had a post-marketing commitment with the original approval to follow a 1,000 to 1,500 patients for five years, looking at the specific safety concerns that were of concern at the time. We did get the five-year data and it was very helpful, and the data were included in the label when they were reviewed. It was similar for elimnab. When etanercept was approved for JRA there was a commitment to follow I believe 500 patients for long term. There may be some other people who know more details about this. Is there anyone else who wants to comment on the Enbrel JRA registry?

DR. GIANNINI: I am Ed Giannini. I am the PI of that registry. We are fully enrolled at 600. Three years of intensive follow-up has given us some very useful information. We haven't really detected any rare side effects that we didn't expect. Nevertheless, we successfully did enroll it. A lot of work. I can tell you the cost of it, which is being paid for by Amgen, is a little over a million dollars.

DR. BATHON: I guess we have taken the stance that registry is the way to look at safety. Does anybody feel that there should be additional double-blind studies with active comparator, or some other placebo-control with option at so many months to roll into active treatment? Is there any thought that additional double-blind trials are important for safety? Dr. Proschan?

DR. PROSCHAN: Yes, they are not going to answer the question because there are just not going to be enough events.

DR. BATHON: For cardiovascular. What about blood pressure, kidney, GI? Anybody have any

thoughts? Dr. Rappaport?

DR. RAPPAPORT: I think that is useful information but I would be concerned that those are still surrogates and we don't know what the long-term consequences of any changes in those two parameters would mean.

DR. BATHON: Yes?

DR. DAUM: I have been impressed by several comments made today by rheumatologic colleagues that they seem to have a reasonable national network of talking to each other and collecting data. I guess the kind of registry I would go for is one that involves then as sort of the anchor, and I guess stress something that hasn't been said that much, that I think the treatment of this disease should be done in consultation with a pediatric rheumatologist. Whether that person is directing the care or initiating the care to be implemented with occasional follow-up consultation, both of those ways would be acceptable to me. If people agree with that concept which, from what I have heard today in this incredibly complicated

disease, and I don't have any personal doubt about it, then they could be perhaps harnessed or fundedB-that would be better, into helping to do a long-term safety analysis in this disease. Whether you call that a registryB-I don't like the word "mandatory either-Bor some king of study where patients are enrolled who are receiving this under the care of a pediatric rheumatologist, I think that is the way to build a study network and collect data.

So, I guess the central point to just repeat is that I think the pediatric rheumatologists should be calling the shot in managing this disease and they would, therefore, be the likely place to initiate this new indication and therapy and collect data about it.

DR. BATHON: So, your suggestion would be that the sponsor sponsor such a registry but work through one of the pediatric rheumatology networks.

DR. DAUM: Well, I take Richard's point very well. I mean, it would be nice to have a comprehensive registry of this disease but I think

that is a much bigger project than we are really probably charged with or capable of recommending today. It would be really great to have a JRA master database but I think today our charge is to look at Celebrex long-term safety. So, whether you call it a registry or a funded study or a mechanism for collecting data, I don't know what the right term is. I am happy to have the sponsor involved in that process. I think they probably, like any good company, need to be regulated and I think that the pediatric rheumatologists are the folks to really drive the patients and drive the data collection. So, that is how I would weigh in.

DR. RAPPAPORT: For clarification, are you suggesting that the product be labeled specifically for use only by pediatric rheumatologists?

DR. DAUM: Can I soften it and suggest that it is suggested that a pediatric rheumatologist be involved in the care of this disease?

DR. RAPPAPORT: Well, we can talk about the regulatory difficulties of doing that but I would certainly want to hear from the pediatric

rheumatologists about whether that is even feasible.

DR. BATHON: Dr. Weise?

DR. WEISE: A comment about something parallel to a registry but for clinical trials, the most dramatic improvements in pediatric disease have been through what I guess the current incarnation now is, the children's oncology group which designs treatment trials for pediatric leukemias and some other cancers. I don't know if it would be feasible to bring all the pediatric rheumatologists together in building treatment strategies. You would end up with treatment benefits as well as data on outcomes and safety in the long term. But that takes money too.

DR. BATHON: I think you already have these mechanisms set up, do you not, pediatric rheumatologists? Dr. Sandborg?

DR. SANDBORG: We do. We have some networks. I think one of the big differences is that the children's oncology group is supported by the federal government and that makes a big

difference in the ability to, from within, grow projects that one thinks are important such as a registry, which are typically not well thought of as a funding opportunity.

I also just wanted to respond to your comment about the feasibility of restricting prescribing practices. I think that we are very concerned in pediatric rheumatology that there are kids who are not being cared for by somebody trained. They may not be a pediatric rheumatologist but somebody who at least has some understanding of the disease process, and that is my, and I think other people share it, one of our major goals in education and outreach and training in the medical centers. But I would hate to restrict access for somebody who lived in Montana where there is no pediatric rheumatologist, or Idaho or Nevada, multiple states. So, it is a real ambivalent sort of issue.

DR. BATHON: Dr. Chesney?

DR. CHESNEY: Somebody mentioned this earlier but I am just thinking out loud, when the

word gets out that this committee approved Celebrex for the treatment of JRA in children, they are going to automatically extend that to, "well, obviously it's safe for me to use for the many things it is already being used for off-label." I was impressed by the reduction in sales after the Vioxx information came out. It was very dramatic. I am just wondering out loud now if we are going to see if the message people get is going to be not the message that we would like to give, in other words, "Celebrex is now safe for use in children. Oh, by the way, they happened to approve it for JRA but that's okay, I'll use it for everything else."

DR. BATHON: We were speculating about that earlier. Mr. Levin?

MR. LEVIN: I mean, I think that is a legitimate concern but I think you have to do a "work around." The "work around" for me is if you approve the new indication you do so with great caution and, again, building in active surveillance that says, yes, we are approving it but we are still really concerned about it and we really want