to get more data before we make up our minds entirely about this venture.

So, I think that is always the risk, and the message you send out is maybe not the message you intended to send out. But I think if we really are convinced that this is the right thing to do, that would be not a good reason not to do it. If the message, again, is cloaked with appropriate cautionary language and action, then I think it may sort of mediate that effect. What the sponsor suggested is not, to me, sufficient to do that.

DR. BATHON: Dr. Weise?

DR. WEISE: A bit of information, if a drug is labeled can it be labeled for an indication that our data supports? Like, could it say it is approved for use short term, and then define what short term is? Like what our data covers?

DR. RAPPAPORT: Yes, you can do that but in this particular case we chose to use the length of this trial to represent chronic treatment. So, it would be difficult for us. I mean, the label will include information about the length of the study

so it is in there. But to specifically put in the indication that this is only for short-term use would be difficult because we felt that this trial represented a reasonable example of long-term exposure.

DR. MEYER: I will just add that in some other chronic diseases like asthma we have in certain sensesB-I should point out that the drugs for asthma are also studied for 12 weeks, although you get a one-year open-label extension trial commonly. In any case, we have had instances where we have not restricted the indication but we have mentioned that the safety and effectiveness beyond a certain point has not been established.

DR. BATHON: Dr. Gorman?

DR. GORMAN: The briefing packet reminded me of my concern about non-inferiority trials and then Dr. Siegel did an excellent job of raising that anxiety even more. When we were talking about other studies that we wanted to do if we were going to ask, I would like to call it an efficacy trial but I really wanted a time-to-treatment failure

trial where you put people on whatever agents you wanted to compare to this agent and then see how long it is until they switch. One of the things I have been impressed with, listening to my pediatric rheumatology colleagues and knowing my neurology colleagues and my asthma colleagues, people switch medicines all the time because it either doesn't work or it has some adverse event, and I would like to see if this drug really is effective, or more effective or more efficacious, whichever word you want to say. That would give me more comfort, whether people go off of it because it doesn't work or whether they go off of it because it has a side effect that is no longer tolerable to them. I think that would be a study I would like to see from the agency.

DR. BATHON: Well, I think we have had an extensive discussion about safety and I am not sure that we have hit on any new points in the past ten minutes or so. So, I think that the majority of the discussion has been on a suggestion of a registry, mainly driven by the absence of long-term

safety data. Is everybody comfortable with moving to a vote? First we will answer yes or no to the question about safety and then, depending on whether the majority is yes or no, we will move to the sub-question.

So, the question is do the available data demonstrate that Celebrex is safe in the treatment of JRA? We will start on this side of the room with Dr. Sandborg. Say your name and yes or no.

DR. SANDBORG: Christy Sandborg, no.

DR. GORMAN: Richard Gorman, no.

DR. DAUM: Robert Daum, yes, for the duration of the study that was observed.

DR. PROSCHAN: Mike Proschan, no, but I think it doesn't demonstrate that it is unsafe either.

MS. DOKKEN: Deborah Dokken, no.

MR. LEVIN: Arthur Levin, no.

DR. WEISE: No less safe than other current uninvestigated agents. Am I allowed to abstain?

DR. BATHON: Yes.

DR. WEISE: Abstain.

DR. MORRIS: Was it yes, short term; no, long term? Is that our vote?

DR. BATHON: I think yes or no is what we want.

DR. MORRIS: Just yes or no?

DR. BATHON: Yes.

DR. MORRIS: No.

DR. HOLMBOE: Yes, only in the time that was studied compared to another agent. That is it.

DR. BATHON: Joan Bathon, no.

DR. CHESNEY: Joan Chesney, no.

DR. LEHMAN: Tom Lehman, I think in the context of the rest of what we do the answer is yes.

DR. O'NEIL: Kathleen O'Neil, a very deliberate and considered yes in comparison to other drugs and the standards we use in other drug approvals.

DR. DAVIS: John Davis, yes in the short term compared to other non-steroidals.

DR. BOULWARE: Dennis Boulware, given the instructions earlier, as compared to the current

medications used I would have to say yes.

DR. BATHON: Dr. Turk, can we get your vote?

DR. TURK: Yes. Can you hear me?

DR. BATHON: Yes, we can hear you.

DR. TURK: Yes in the context of the short duration.

DR. BATHON: So, we have eight "no" seven "yes" and one abstention. Do we move to the sub-question? That is a pretty tight vote. If we voted no, what additional studies should be undertaken? We kind of talked about that. If yes, do you recommend any phase 4 studies? I think we have kind of discussed those anyway, no matter what. I don't think it matters.

So, we move to the last question which is really more difficult, is the risk/benefit ratio of celecoxib in the treatment of JRA adequate to support the approval of the product for this indication?

I am not sure whether we need any more discussion at this point since we have discussed

each issue separately and now you just need to weigh them together. Dr. Siegel?

DR. SIEGEL: Could we go back to the previous question?

DR. BATHON: Please.

DR. SIEGEL: Since many of people in fact voted no, I think that first sub-bullet is relevant. To restate it, if I may, it would be if the vote is no, what additional studies if positive would allow the vote to change to yes, for example at a subsequent advisory committee?

DR. BATHON: Anybody want to address that? We discussed the registry but that is obviously a long-term endeavor. We discussed time to fail study design but that doesn't really address safety as much as possibly efficacy. Dr. Boulware?

DR. BOULWARE: I wonder if it wouldn't be more helpful to the FDA and yourself if you split the first question up and asked us again in terms of short-term safety and long term. I think many of us are comfortable with short term but uncomfortable with the long term. Then they can

decide if they want to add things to the labeling.

DR. BATHON: The only problem I have with that though is whether it makes sense to approve a drug for short term that is chronic.

DR. BOULWARE: But then it would lead you to the next question of what do we need to be more comfortable about long term and that would help them also.

DR. MEYER: But I can tell you from the agency's experience that even if we say you should not use it beyond, say, two weeks that is not paid attention to. So, from the approval decision for a chronic use drug we are basically asking is there enough safety information for you to say yes to question two for a chronic use drug.

DR. BATHON: And, I think if somebody voted yes to efficacy, no to safety it doesn't preclude them from voting for approval, either way, so you are not necessarily saying that you disapprove either. Dr. Morris?

DR. MORRIS: I guess my confusion is, I mean, looking at the next question, should the

product be approved, and my discomfort is not whether it is approved or not but what the post-marketing commitment is going to look like. That is where I get confused in this question about safety or not. If we say it is not safe, unless there is post-marketing surveillance dataB-I guess that is where I am having problems with these questions.

DR. MEYER: Well, I think for a question like number three, if you want to move towards that, we are asking based on the information available to date. We are very much hearing and we will take under very serious advisement the advice that is being given to us about the need for further characterization of safety in the post-marketing setting. But you shouldn't use the availability of that data at some point in the distant future, if ever, as a basis for answering yes or no to question three. You should use the data that is available in adults with this agent, the data that are available for this agent in children, the data that are available for the

alternative therapies in children and the data on the efficacy of this in children to sort of synthesize your answer to number three.

DR. MORRIS: Just to summarize so I make sure I understand what you just said, we make the assumption that there will be post-marketing data in some way as part of the package that the company has to agree to get the drug approved. But in this vote we are just saying as of right now, without those data, is it safe or not.

DR. MEYER: Precisely. I am not saying it that way so we are sort of escaping any obligation--

DR. MORRIS: No, I understand.

DR. MEYER: B-or any plan to work with the sponsor, if you were to vote yes or to recommend yes, to institute post0marketing assessments but as of today, with what you have heard, with the lay of the land, answer question three without regard to whether there are post-marketing studies done.

DR. BATHON: I guess we are evaluating safety in the current climate in a study that has

yesterday's design. That is the other problem.

DR. MEYER: Welcome to our world. Yes, I think the one difficulty that we are going to get, and maybe we can come back to this depending on how question three comes out, but if, in fact, we get a no recommendation we are still stuck with a seeminglyB-contingent on the answer to question two where at least by a slim majority is the answer is that there is not sufficient safety, but I have not heard much in the way of a real answer to Dr. Siegel's question, which is if the recommendation is no, what can be done to fix that prior to approval? Most of what we have heard about is what would be done after approval, which is very different.

DR. BATHON: Dr. Gorman?

DR. GORMAN: I think in explaining my "no" vote I would like to say that the time horizon of the study and the time horizon to cardiac events seems to be too short to know if there are any cardiac events with this. So, that is why I said it wasn't safe. The question says do you think it

is safe in the treatment of JRA. It doesn't say is it safe forever or is it safe enough to approve. I think that is a question that in the vote that says "no" is completely safe or safe in the long term is also to say no, that there is a little bit more pressure on the agency and the sponsor to generate the long-term data that we just spent an hour talking about.

DR. BATHON: I was having trouble hearing you.

DR. GORMAN: I am sorry.

DR. BATHON: Can you make your suggestion louder and shorter?

[Laughter]

DR. GORMAN: Louder is easy! The "no" vote was because the safety data did not extend long enough and, therefore, I felt uncomfortable voting that it was safe when I don't have long-term data. The "no" vote was a method of trying to express the concern of this member on the committee that the long-term data should be generated.

DR. BATHON: That was also my stance and

that is why I think you could still vote for approval but give the message that the safety needs to be enhanced upon, or something. Mr. Levin, you wanted some clarification, or did you get it?

MR. LEVIN: The other consideration, and we haven't talked about it really, is do you approve something with a risk management strategy in place. I don't know if that applies. I mean, that is another way to do it. Right? I mean, if we could devise one that would try to limit risk that we thought--

DR. MEYER: What risk would you be limiting?

MR. LEVIN: I don't have much to say but it is a third--

DR. MEYER: Yes, but, again, I think in terms of an up/down since almost all these things that we are talking about are ultimately voluntary mechanisms and, in fact, they are not going to be-Bif you look sort of at the use pattern of a drug, it tends to be very high in the first few years after approval and then sometimes will slip

as other alternatives become available. So, you are talking about the time where the maximum exposure to the population would be the area where you have the least certainty. That is why I am saying that for question three you really have to do that without respect with what might be learned down the road.

DR. BATHON: Dr. Daum was next.

DR. DAUM: My colleague explained his "no" vote and I will explain my "yes" vote the same way. I think that, "yes" is based on the relatively short-term data that we were shown but it was also based on Dr. Meyer's comment that this is a fairly standard kind of length of study and that something could be put in the package insert saying that the safety beyond this time has not been established. So, I guess I am thinking about those three points together in determining that, yes, it appeared to me as safe as other comparable therapies that we were shown today.

DR. BATHON: Yes, I think I a sense we are saying the same thing but with a different answer.

DR. DAUM: That is exactly why I wanted to say it out loud.

DR. BATHON: And some of the newer NSAID trials in adults are of a much longer duration, a year, which in adults might be long enough to uncover cardiovascular risk but in kids it is not clear that even extending a longer study would answer that.

DR. MEYER: I just wanted to be clear about one thing too so that I am not misunderstood. In terms of this sort of being the standard amount of data, at least with the children studied in this kind of setting we look also at what is known about the safety in adults. You know, we are not saying that children are just little adults and, you know, there could be differences that show up. I understand all that. Still, there is information from the adults that at least can inform some judgment about the safety in children. So, that is something the FDA does take into consideration in looking at pediatric indications for drugs where the adult indication is already well established

and well studied.

DR. BATHON: Dr. Lehman?

DR. LEHMAN: I think we need to be careful here because none of us is going to be able to forecast the future 10 years in advance or 20 years in advance. And, even with the drugs that we know are toxic when given to children, they are not having problems in childhood. We may be presenting an impossible hurdle here. We would like to all know that 20 years from now we won't regret today's decision and that is impossible. The drugs that we know, like the steroids, that do cause problems are not causing problems that are going to be found in a three-year study or a five-year study; they are showing up when these children are between 20-30 years of age and that is more than 10 years after most of them have been treated.

So, if we decide that we need to say we can't prove something is safe because we can't see 20 years into the future, we are going to have no drugs for our kids. So, I think we need to be very careful about the hurdles we are presenting here in

terms of what we are defining as safe. There is actually a tremendous amount of experience with Celebrex both in the adult literature and in the pediatric literature and, given the numbers it took to recognize the cardiac risk in adults, I don't think we will ever reach those numbers in any pediatric study.

DR. BATHON: Dr. Siegel, did you still want to comment?

DR. SIEGEL: I am not sure if this comment is still necessary, but I wanted to maybe talk a little bit about the logic of the three questions. It may have been clear to some people, implicit for others but not necessarily clear.

The Food, Drug and Cosmetic Act says that the agency should approve drugs that are safe and effective so the logic of the three questions is, first, we are asking the committee's input on whether effectiveness has been shown, or efficacy. The second is has safety been shown? The third, given that all drugs, including this one, have some toxicities, what does the risk/benefit profile look

like? Maybe that was obvious to everyone but I want to make it clear that that is what we are asking for with question two. I guess somehow mixing in the question about mandating long-term studies or should we wait for 10- or 20-year studies to demonstrate safety got mixed in and may have led to some lack of clarity in the intent of the question.

DR. BATHON: Do you think the question should be reworded given all this discussion and potential confusion? There was a suggestion to break it into two questions.

DR. MEYER: I definitely don't want to break it into short and long term. I would suggest that we perhaps move on to question three because ultimately it is the synthesis question that is the important one.

DR. BATHON: Is there interest, or precedent, or is it allowed, does anybody want to consider re-voting on safety given this discussion? Is that allowed? Is that anybody's interest?

DR. MEYER: I think we are fine.

DR. BATHON: So, we will go on to the third question. Is everybody ready to vote on the third question? Is the risk/benefit ratio of celecoxib in the treatment of JRA adequate to support the approval of the product for this indication? We will start on this side of the room with Dr. Boulware. Is there any discussion?

DR. WEISE: I will try to be short--

DR. BATHON: If it is a new point because I think we are rehashing--

DR. WEISE: Yes, just to sort of put on the ethics hat, I think one thing that strikes me when I read question number three on risk/benefit ratio is that there may be a different way we need to think about risk and benefit with all of the uncertainties that we have had here, and that is to recognize that maybe we need to be talking about burdens of disease versus benefit of this particular drug, and what we are talking about is a burden over an entire childhood and comparing that to a risk that may be long term and outside of childhood but still a hypothetical risk, and then

throw into the mix that we don't really know how much Celebrex diminishes the burdens of disease in this entire childhood. Okay? So, it is not a single point in time but it is a huge issue with a lot of emotion behind it, and style of treatment, etc., etc. And, it makes me think that maybe long-term risks might become more acceptable if you have choices of treatment modalities that might make the middle term burdens a lot lessB-just to muddy the waters.

DR. BATHON: Dr. Morris, last comment?

DR. MORRIS: I wanted to respond to the very specific question that Dr. Siegel brought up about what to do now and what to do after approval. One of the things that can be done now, if it hasn't been done already is, because there is use in children already of this drug and there are databases that probably track that, it is possible to look at a case-control study comparing long-term use with naproxen and looking for comparability, especially with people who have used this drug for six months to a year as opposed to less than six

months. So, I would be a lot more comfortable if that was looked at prior to approval and it was shown that there was some indication, based on a database analysis, that there was comparability in longer-term safety with naproxen prior to approval.

DR. BATHON: So, you are suggesting like a one-year study?

DR. MORRIS: It is a retrospective study.

DR. BATHON: Retrospective?

DR. MORRIS: Yes.

DR. BATHON: All right. So, we will proceed with our vote. Dr. Boulware is on the hot seat again.

DR. BOULWARE: Thank you. Dennis Boulware, I vote yes only if they do long-term safety studies.

DR. DAVIS: John Davis, given the burden of disease, the limited treatment options available for the patients, the short-term safety data that we have been shown here and potential labeling for unknown long-term use, as well as no other signals in other sources, including adults, and also

post-marketing surveillance, I vote yes.

DR. O'NEIL: Kathleen O'Neil, yes, with the same qualifications.

DR. LEHMAN: Tom Lehman, I have said my piece. Yes.

DR. CHESNEY: Joan Chesney, yes, with the same qualifications already well articulated.

DR. BATHON: Joan Bathon, yes, with the same recommendations, a strong recommendation for long-term safety.

DR. HOLMBOE: Eric Holmboe, yes, strong recommendation for long-term safety as well.

DR. MORRIS: Lou Morris, yes, etc.

DR. WEISE: Kathryn Weise, yes, same recommendations.

MR. LEVIN: Arthur Levin, no.

MS. DOKKEN: Deborah Dokken, yes, with everything that Dr. Davis said.

DR. PROSCHAN: Mike Proschan, I think it is probably as adequate as what was used to approve naproxen. So, yes, but just barely.

[Laughter]

DR. DAUM: Robert Daum, yes, and echoing word-for-word the comments of Drs. Davis and Boulware.

DR. GORMAN: Richard Gorman, yes, with all of what Dr. Boulware said plus a little plug for my rheumatology friends, which is that I trust in the wisdom of the marketplace and the astute clinical judgments of my pediatric rheumatology colleagues to see whether this drug really is better for children as time marches on.

DR. SANDBORG: Christy Sandborg, yes, with the recommendations that have been already articulated.

DR. BATHON: So, we have 14 "yes". Oh, Dr. Turk?

DR. TURK: Yes.

DR. BATHON: Yes, so 15 "yes" and one "no" with all of the attached recommendations. I think that concludes our meeting. Anything else from the FDA? Have you had all your questions answered as best as we can? Any other issues?

DR. MEYER: I think so. I just wanted to

take the time to thank you for your conduct of the meeting and thank the sponsor, and particularly the other advisory committee members and SGEs who are serving today for their thoughtful input and their advice to us. So, thank you very much.

DR. BATHON: I would like to thank everybody as well. Ms. Dokken has one final comment?

MS. DOKKEN: I didn't know we were ending quite so abruptly. Is there some assumption that the long series of recommendations we added to question three will be worked into the labeling?

DR. MEYER: Obviously, you are an advisory committee. We heard very strong recommendations in this regard and we will take that under very strong advisement.

DR. BATHON: Thank you again.

[Whereupon, at 4:09 p.m., the proceedings were adjourned.]

- - -