before, so I'll just leave it.

DR. HECKBERT: Susan Heckbert. I voted yes that there is sufficient information regarding what looks like an increased risk of malignancy to make me concerned about that. So it's sufficient for that. But of course, it's not sufficient to know what is the risk, to define the risk in pediatric psoriasis. Of course, we need more information about that. So again, it's hinging on the meaning of the word "sufficient."

DR. DRAKE: Lynn Drake. I abstained, mainly because of the monotherapy issue. It was -- the data was confusing to me because it had so many variables in it. And therefore, I couldn't separate it out adequately. Thank you.

By the way, my vote was consistent with all the yeses and noes and the explanations given around the table, and the abstention.

DR. CRAWFORD: Stephanie Crawford. I voted no. I based this largely on everything

said. Plus, if I look at Slide 103 from the sponsor, the sponsor says, "An increased risk of malignancy can neither be confirmed nor excluded."

DR. BIGBY: We'll go on to Question 7. The applicant has agreed to conduct post-marketing safety study 20040210. This long-term study is intended to provide safety information regarding the use of etanercept in adult patient. Does the Committee recommend approval of etanercept in pediatric patients prior to the completion of this safety study? And just for clarification to this sponsor, what is the current status of this study?

DR. SEVERINO: The study is fully enrolled, and five-year data are expected in the time frame that the Agency mentioned during their presentation.

So follow-up is ongoing.

DR. BIGBY: The "n" in the study is what? And the completion of enrollment was when?

DR. SEVERINO: The total patients enrolled were 2,511, with a target of 2,500.

DR. DRAKE: The year was 2013, wasn't it?

DR. SEVERINO: Yes. And the completion of enrollment was on the -- the beginning of enrollment was May 31, 2006; completion of enrollment was November 29, 2007. So five years of follow-up will be available in November of 2012.

DR. BIGBY: The question is open for discussion.

DR. HECKBERT: Yes, and --

DR. BIGBY:: Thank you very much.

DR. HECKBERT: Because I get the various studies mixed up. This is a study of adult patients with what?

DR. SEVERINO: This is adult patients with moderate to severe plaque psoriasis.

DR. HECKBERT: Okay.

DR. DAUM: Can I ask how the voting part of Question 7 differs from Question 9, just

for clarification?

DR. WALKER: The information we're interested in from the Committee with No. 7 is, this is the monotherapy study for psoriasis patients. So it's difficult to know where to put some of these questions. But this would assume if the Committee's going to recommend approval, where do you want the outcomes from the study to be, before or after approval?

DR. DAUM: That's a helpful clarification.

DR. BIGBY: Further discussion?

I'm loving it.

Does the Committee recommend approval of etanercept in pediatric patients prior to the completion of this safety study?

Those voting yes, raise your hand. Those voting no, raise your hand. Abstentions? One.

So the tally is nine yes, three no, one abstention.

Dr. Katz.

DR. KATZ: If we don't recommend this on the basis of until that safety study's done, it's delayed, I think we can allay our anxiety by having a sufficient warning in labeling that safety hasn't been determined in malignancy. So that would I think take care of that.

I should have said I voted yes.

DR. STERN: I voted yes because --

DR. BIGBY: Name, name.

DR. STERN: Sorry. Rob Stern. I voted yes because I'd like decisions to be made in my lifetime. Even more importantly, I'm quite frankly quite skeptical that this study will lead to any robust conclusions. And so I don't think we'll have additional robust information in 2013.

DR. O'NEIL: Kathleen O'Neil. I voted yes, because post-marketing surveillance for rare events is going to prove that they're rare. It may indeed prove that there's a risk ratio in adults, but the risk ratio in adults for cancers that are more prevalent in adults than in

children is not really going to be that informative. And so I think it's unconscionable to withhold something based on whether it works in adults or not, or is safe in adults to some extent, while we wait for five more years.

DR. MAJUMDER: Mary Majumder. I voted yes, because I heard 2012 as the completion date. And I heard from the public that if this Committee doesn't approve, that may make access harder, even for patients who I think access is probably justified because their condition is severe. And even if this bears out some of the concerns -- the study -- they're still not, probably, going to be huge.

And so I'm looking at patients possibly losing access to the drug or not getting it for many years, so that we get information that may or may not ultimately bear on the issue. I think it's difficult.

DR. BIGBY: Michael Bigby. I voted no because I think many of our deliberations are hampered by the lack of information. And I

don't think delaying use of this drug for five years, given its degree of efficacy, is such a terrible thing. Also -- you know, in terms of serious infections, death is irreversible.

DR. THIERS: Bruce Thiers. I voted yes. I think at some point we have to deal with the information we have at hand. And for the reasons that were already mentioned by some of the others, I think now's the time.

DR. LEVIN: I voted yes, although I continue to think the question sort of is entrapping. And if I were arranging the questions, I would have asked -- up or down, do you approve or don't approve. And then under what conditions. I would just agree with Bob Stern's comments.

DR. DAUM: I'm Robert Daum. I voted yes, and I agree with Dr. Levin's comment. I interpreted the question the way the Agency redefined it for us.

And that is to say, if we were inclined to approve of it, do we need these

data from the adult safety study to say to do it now. And I don't think they're going to be all that informative, as others have said around the table. So I would be able to make my decision now without those, although I'll look at them with interest.

DR. CRAWFORD: Stephanie Crawford. I'm the one who abstained, largely because of what my colleague, Art Levin, said, because I think the contingency makes it a leading question. So regardless of the long-term -- the data that will be available November 2012 at the earliest for the adult patients, I don't think that has a bearing on the first part of the question for me.

DR. DRAKE: Lynn Drake. I voted yes, because -- I mean, while acknowledging the risk, I think that the study five years from now isn't going to give us that much information. I agree totally with what Dr. O'Neil has said, because kids are basically different than adults, and malignancies behave differently. There's a

whole pattern of difference. So I'm not sure it would add that much.

The second reason I voted yes was, what I'm seeing right now is a lot of off-label use. Not only of this drug, but of a lot of other potentially very toxic drugs, in this population in particular. And I guess I would rather see things formalized, or that we have an opportunity to track it, you've got a more formal opportunity to have a reporting mechanism, it comes under surveillance that way, with it approved. You know?

I guess I would like to see -- stuff's being used, so let's have it being used in an organized fashion, so we can actually get some answers to these questions.

DR. HECKBERT: This is Susan Heckbert. I voted no on this question, partly for the reasons Dr. Bigby gave. I agree with Mr. Levin that 7 and 8 are tied together, and that's part of why I voted no, in that I don't think we

should approve this drug for moderate plaque psoriasis in children. So if that's the indication we're voting on, then I need to vote no for 7.

DR. RINGEL: Eileen Ringel. I voted no for several reasons. First of all, special caution needs to be taken in approving drugs for children. Remember, if you have a four year old and mommy is consenting for them, and that child is going to grow up and be 34 and may be very, very angry if they find out they have a significant risk of lymphoma and had nothing to say about it.

Secondly, we're not withholding the drug. It is available off-label. We're not making it any worse than it is now. And thirdly, the FDA mandated this follow-up study. If we were so convinced that it's worthless, we shouldn't have mandated it. I think the least we can do is wait for the results.

DR. SHWAYDER: Tor Shwayder. I voted

yes. And interestingly, I agree with both Drs. Thiers and Bigby, who voted in opposite directions. Hopefully, intelligent decisions are made by well-informed doctors and patients. Based on the data and risk that we know at the moment, that's about the best I could hope for.

DR. BIGBY: Question 8. So the section is: please discuss the relative benefits and risks for the use of etanercept in pediatric patients.

Question 8 is: do the benefits of etanercept therapy in the treatment of children with moderate to severe plaque psoriasis outweigh the risks?

DR. WALKER: I think, like yesterday, if you look at 8 and 9 together, 8 gives you the opportunity to have discussion, and then you can move on to 9. So I don't think -- you know, think of it in that vein. Eight is designed to elicit the thinking and discussion from the members behind their vote on 9.

DR. LEVIN: Point of information. So

we've heard a number of expressions of concern about the indication: severe, severe to moderate, severe only. How would that factor into these -- I mean, how would you see that factoring into these questions? Because right now, if one said -- I would say that the benefits outweigh the risks for severe, there's sort of no place -- I mean, you'd have to vote no, period.

DR. WALKER: I think you could give us that information as you frame your answer. Because if you voted yes, provisionally, with something -- or no -- because I think that's all useful information. It's not just the outcome of the vote that is of import to us, it's the entire discussion.

All of it's valuable.

DR. BIGBY: Rob.

DR. STERN: One important thing, though, from my perspective, is, as I recall, nearly two-thirds -- the only somewhat surrogate measure we have of severity was the Physician's

Global Assessment. And as I recall, about two-thirds of the individuals were a 3, which most people would say is in the middle of the scale, and therefore moderate. That means I wonder, and in fact, I would like to see whether for 5s alone, or 4s and 5s, at least by that criteria, that in the 12-week trial, we even made significance.

So if you're going to only approve it for severe, both the efficacy and the safety data would be coming from -- at least by my best guess, only about a third of the enrolled patients, about 30 or 35 in each arm, which is an extraordinarily low database. We can't take data from the moderates to approve it for severes. So it's a real conundrum.

DR. BIGBY: Dr. O'Neil.

DR. O'NEIL: My question was for the dermatologists, being one of a few who are not on this panel -- is there a definition, a working definition, of what is severe and what

is moderate psoriasis?

DR. BIGBY: Absolutely not.

DR. SHWAYDER: I doubt there is, but I know that the company did the data for 4s and 5s. They had number crunchers do that. If it didn't show anything, will never come to light. So I want to ask industry, in front of everybody, did you do the datas on PGA 4s and 5s?

DR. SEVERINO: Can we bring the slide up, please?

This slide shows PASI 75 for subjects who are at 3, and greater than 3, so that's the 4s and 5s in the crosshatch. And as you can see, the responses were consistent between those two groups. If we look at the 4s and 5s, 64 percent achieved a PASI 75 at week 12.

DR. THIERS: What's the N number?

DR. SEVERINO: We can get that for you in just a second.

DR. HECKBERT: Yes, we need both Ns

and statistical significance. I suspect it is significant, but I'd like to know that.

DR. THIERS: I would have guessed that the results would be more striking with the more severe patients anyways. This is not really surprising, what we're seeing.

DR. KATZ: I'd like to make a comment to Dr. O'Neil's comment, and respectfully disagree. It's not quantitative, severe and moderate. But we all know -- all the dermatologists here do know -- what severe psoriasis is. 80 percent body involvement is severe psoriasis. What the person, Kelsey, mentioned, pictures -- all over the face, severe psoriasis. 10 percent of body involvement, which we've been dealing with yesterday and today, is not severe psoriasis. That's moderate at the most.

DR. BIGBY: But Robert, many people, many dermatologists would call -- I know I shouldn't do this, but I'm going to tell you a joke.

What is the definition of minor surgery? Minor surgery is surgery --

DR. STERN: Surgery on someone else.

DR. BIGBY: On someone else. Right. No, I'm serious. This is actually serious. So as a child or a parent, what is the definition of mild psoriasis? It's psoriasis that somebody else has.

DR. KATZ: To some extent. But we all would agree with -- I think we could agree on severe psoriasis involving 75 percent of the body. And in general, something like 10 percent is better not to have, but I don't think we'd call it severe.

DR. THIERS: But I think it depends on where it is, where that 10 percent is.

DR. DAUM: Do the dermatologists take into account patient or parent anxiety when they score this? I mean, it's not just -- it seems to me we're just talking about skin, here, and someone who can't go out on Saturday night because their face is covered might be different

than someone who can.

DR. STERN: So that's the impossibility, as Michael says, of a sensitive and specific definition of severe. I should have been, yesterday, seeing psoriasis patients instead of being here. And I've done it for 35 years. And the answer is, as was talked about, for some individuals, it's really a benefit-risk question.

Because for some individuals, relatively small, extensive body surface area, sometimes even in non -- in areas that most people don't see, can be really life-impacting. For other individuals, large, extensive psoriasis that go on to exposed areas, are -- when you ask them about it -- I often ask patients -- I deal mainly with adults -- in fact, almost exclusively with adults, expect for my psoriasis patients -- but I ask adults, so, in the five things that bother you most in your life today, is psoriasis one of the top five? If

they say no, it's not one of the top five, then I try to take systemic therapy off of it. And then we have to go up there. Where does it rank? Because it's really the impact of the disease that will vary among individuals -- and over time, within individuals. That's why Michael's absolutely right. There's no good definition.

However, when you look at these pictures and you look at the PASIs, you can say -- at least in adults, and I don't treat enough children -- that many of those individuals, as adults, in my practice in Boston, would say yeah, I'd rather not have it, but it's not such a big deal. It's something I'd -- it wouldn't make the top five in terms of concerns in their life.

DR. LEVIN: I'm not bothered by this discussion. I think the message that gets sent in labeling to prescribers is sort of guidance.

And if non-clinical -- I mean, they're not non-clinical, but if a -- you

know, all these other sort of social, emotional issues are part of how a clinician evaluates a patient and sort of comes to some conclusion about severity, so be it. The message is that these should be patients that you consider to be having a severe -- you know, have a severe problem. And those are the ones that -- you know, should be treated.

So the fact that there's no magic -- you know, that we're not supplying that means this number or that number, I don't think is bothersome.

Again, it's sort of the principle of the thing, that you're saying there are unknown risks here, and when you use this product, you should be treating a severe -- you know, a patient who you consider to be severe.

DR. KATZ: Why don't we leave the word "moderate" out of it?

DR. BIGBY: Bruce, you want to make a comment? And then I think we should put it to

the vote, and then have people sort of make a statement about this.

DR. THIERS: Yes, yes. Yes. My comment was just did we have the N on the number of 4s and 5s.

DR. STRAHLMAN: While the slide is coming up, could I make a comment?

DR. BIGBY: Yes.

DR. STRAHLMAN: Yes. I just -- in framing it to the point that was made by FDA in answering the question, since definitions of moderate and severe vary greatly in terms of patient assessment, which is really the business that you're in when you're going to prescribe a drug like this for children, I would just ask the Committee to consider, before they would consider separating moderate and severe, as to what the label might look like, and understanding the high likelihood of black boxes and lots of other warnings.

To the point that was made by -- especially some people in the public

forum, if we take "moderate" out, will this be a problem for access and coverage?

So depending upon which way the Committee decides to make a recommendation, I would just ask that that consideration also be in your thoughts.

DR. THIERS: I think what would happen, just in my opinion, is that the insurance companies would define "severe" for us. They would say severe means 20 percent of body surface area.

DR. STRAHLMAN: Exactly. If you don't want that to happen, perhaps you might consider how you want the label to look.

DR. LEVIN: Can I just --

DR. BIGBY:: Go ahead.

DR. LEVIN: With all due respect, while I think that's a real issue, and certainly one I'm concerned about, I don't really think that's how we're supposed to make the decision, as to what the effect of our decision is on the decisions made by insurance companies. I mean,

at least it's never been in other panels I've been on. And the whole issue of cost and availability I think has been avoided by FDA because it has no authority. Am I right? That's not part of the equation.

DR. WALKER: That's not part of FDA's authority. That's correct.

DR. BIGBY: Go ahead, Lynn.

DR. DRAKE: I agree. I mean, having been sitting in Michael's chair, it is not something that's usually considered. So you're exactly right, Dr. Levin.

But I do want to agree with my colleagues that a tiny amount of psoriasis in the wrong place can be as devastating as a whole mess of psoriasis in other places. If you think about it, if it's on your hands, and it can be debilitating. There are body areas that really do impact. So I think it's very tough to sort out moderate from severe.

DR. BIGBY: And the answer to the question?

DR. SEVERINO: The answer to the question on the Ns is that there were 36 in each group.

DR. BIGBY: And the --

DR. SEVERINO: Etanercept and placebo that were 4 or 5.

DR. BIGBY: And the significance?

DR. SEVERINO: We did not test statistical significance for the subgroup analyses, so I don't have that for you today.

DR. BIGBY: We'll put this question to the vote. Do the benefits of etanercept therapy in the treatment of children with moderate to severe plaque psoriasis outweigh the risks?

Those that are voting yes, raise your hand. These are the yeses.

Those voting no, raise your hand.

And abstentions?

So the tally is seven yes, five no, one abstention.

We'll start with Dr. Shwayder.

DR. SHWAYDER: I always like it when

you start on the other side because I can hear the thread of.

I voted no. It just worries me someone with a tiny bit of psoriasis getting etanercept, getting TB, and collapsing on me. I don't think I'd be able to look myself in the mirror.

DR. RINGEL: Eileen Ringel. I voted no because I don't want us -- I don't want people with moderate -- true moderate psoriasis, whatever that is -- to be treated with this drug until we have more information on it. I think that the idea of basing our decision in order to dissemble for the drug company is a really bad precedent. I think we need to convince the drug company to deal with the truth rather than to fool ourselves, or to do an end run around it. I think that's a real bad idea.

DR. HECKBERT: Susan Heckbert. I voted no for the same reasons as Dr. Ringel, and because I don't think the label should read "for the treatment of moderate to severe plaque

psoriasis." Although I do acknowledge that defining what "moderate" is and what "severe" is is tricky.

DR. DRAKE: I abstained, because again, knowing risk and benefits at this point in the game are very difficult. And I would probably be inclined to tell my patients I don't know the risk and benefits, but here are the worrisome things we'd have to follow out. I don't think we have any absolutes on that particular issue, and I think it's a separate issue as to what one would recommend to your patients in terms in treatment.

I mean, I could easily sit down and tell my patient I just don't know. And that's the way I feel right now. It's going to need more information, but it's going to take time to develop that.

DR. CRAWFORD: Stephanie Crawford. Yes, because I believe the benefits will outweigh the risks through appropriate and conservative use that will be better defined

before -- I hope before ultimate approval. I'm sorry, in a risk management plan.

DR. DAUM: I voted yes, and I --

DR. BIGBY: Name.

DR. DAUM: Sorry. I'm Robert Daum.

I voted yes because -- and I guess I would hope that this was limited -- a drug that received very narrow use, and I would hope that it would be limited to severe disease. I include in severe the skin involvement and the patient's feeling about the skin involvement, and I think it's going to have to be left -- I would like to leave it to physician judgment and parent judgment, and child if they're old enough to assent judgment, to decide what "severe" means.

I would certainly make it mandatory to do a PPD before it was started. I would certainly point out to the patient before it started that there is a substantial risk that the child will not respond to the therapy. I would point out that of those that do

respond, that there appears to be almost like a worsening -- a waning effect with time. I would further point out that there's a lot of things we don't know about the safety, including the risk of severe infection, including the risk of malignancy.

I still am persuaded that with the data that we saw about effectiveness -- and I guess, by some of the testimonials we heard this morning, that there are a few, selected patients -- I hope they'd very few -- that would benefit from having this drug, receive an indication while ongoing assessment is occurring.

I'm very concerned about the safety and the possibility of high use, but I think in severe patients, I'd like to see it available. So I voted yes.

DR. LEVIN: Arthur Levin. I voted no, because I remain concerned about the tradeoff between benefit and risks and the safety concerns, because I really would like to send a

message in the labeling to prescribers that it only be used in severe cases -- as broadly defined, not by a number -- but in the clinician's judgment and the patient's judgment. That's what severity means to me.

DR. THIERS: Bruce Thiers. I voted yes. I think the benefits do outweigh the risks. I also considered what else is out there for kids with bad psoriasis, and I think those drugs, in my mind, are potentially more toxic than etanercept. So that, to me, was part of the equation.

I don't think this is going to have widespread use. I think there are only a selected number of children out there who are real candidates for systemic therapy. And I think my colleagues in dermatology will use the drug wisely. So I think overall, the benefits do outweigh the risks.

DR. BIGBY: Michael Bigby. I voted no. Risk-benefit analysis involves assessment of the disease, morbidity and mortality, as well

as the severity and efficacy of the drug; and I think if you put all those things together, the answer is no.

I do think that there will be sort of an indication creep. And I think we'll be surprised at the number of sort of mild to moderate psoriasis children that get treated with the drug.

DR. MAJUMDER: I'm Mary Majumder, and I voted yes. I think, once again, there's almost no distance between the yeses and the noes. Nobody wants this to be used widely, and nobody wants it never to be used in the pediatric population no matter what. And so, given all that, and the eloquent testimony we heard earlier, I think conditions that we're going to impose, or at least request or recommend that FDA impose, I have to end up favoring sort of the side that says -- you know, do everything you can to be transparent, to warn people about the problems that may exist, to monitor, to study, to update, but allow some

discretion for physicians and patients and parents to make ultimate risk-benefit assessments in the individualized context.

DR. O'NEIL: Kathleen O'Neil. I voted yes, and I have a somewhat unique perspective because I have been prescribing this drug for 10 years for children with Juvenile Arthritis. I have this discussion about risk and benefit every time I prescribe it, and actually, every time I renew the prescription, pretty much.

And I also know that the marketplace, particularly the third-party payers, are going to regulate its distribution as well. And it will be restricted to the more severe cases, at least for the first 5 to 10 years. It is very difficult to start a patient with severe polyarticular Juvenile Arthritis on any drug that is off-label, currently.

You can start it in -- you can start etanercept now because it is now labeled, but if you have someone with severe

disease who is under the age of two, you have to get a written decree from God, which is hard to get these days, at least in my life.

I think we have sufficient evidence that there is a need. We have sufficient evidence of efficacy. I think there are very severe and very serious risks that need to be monitored for and need to be discussed with the patients. I would like to see the word "severe" rather than "moderate to severe," I think, because -- and leave that to the discretion of the prescribing physician, because severity, as we said, can be affected by a number of factors.

DR. STERN: Rob Stern. I voted yes, with extreme ambivalence. Basically, we should be data-driven, and all the data comes from a trial of moderate and severe, with no way of retrospectively, for all the reasons we've said, redefining these individuals. So to me, it was really, do we have sufficient information to label this drug if we do it right? And I must

say that once we've said this, if there was a motion to limit the initial approval to severe, I would vote for that in a Manhattan second, or whatever the expression is.

SPEAKER: New York minute.

SPEAKER: New York second.

DR. KATZ: Robert Katz. I voted yes because the drug has to be made available. It is already available off-label. I think it was very clearly stated by Dr. Eichenfield, or admitted by him, that it would be just for a small portion of the population. Efficacy was clearly shown with both Global and PASI. It wasn't the majority, as was mentioned, but it was a good 35, 40 percent.

As far as risk-benefit, that's to be determined, and that, we share with our patients with everything that we prescribe, not only in this disease, in everything. It's risk-benefit. And that's for the physician and the patient to make the determination together.

I would also love "moderate" to be out, and I retract my argument before, defining it as percentage of body involvement. But it has to be considered severe by patient and doctor. So I would omit that word "moderate."

DR. SHWAYDER: What was the final tally?

DR. BIGBY: Seven yeses, five noes, one abstention.

I think I'm going to go ahead and call for a vote on Question 9. Should etanercept be approved for the treatment of moderate to severe psoriasis in children?

I think the vote will go pretty much the same way as 8. All those voting yes, raise your hands. Yeses. Those voting no, raise your hand.

The final tally is -- there are no abstentions. The final tally is eight yes, five no, no abstentions.

We need to go around and just

identify yourself and your vote, starting with Robert Katz. And what I would say about comments is, if you -- I think we've said most of what we want to have to say, so.

DR. KATZ: I agree.

Robert Katz. Yes.

DR. STERN: Rob Stern. Yes.

DR. O'NEIL: Kathleen O'Neil. Yes.

DR. MAJUMDER: Mary Majumder. Yes.

DR. BIGBY: Michael Bigby. No.

DR. THIERS: Bruce Thiers. Yes.

DR. LEVIN: Arthur Levin. No.

DR. DAUM: Robert Daum. Yes. And I would like to see a straw vote, at least informally, when we're done, about how many would prefer the word "severe" over "moderate to severe."

DR. BIGBY: Actually, we get to that in 11, I think.

DR. CRAWFORD: Stephanie Crawford. I voted no for that exact reason. The question is moderate or severe, and I would just favor

severe.

DR. DRAKE: Lynn Drake. Yes.

DR. HECKBERT: Susan Heckbert. No.

DR. RINGEL: Eileen Ringel. No.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BIGBY: Susan, I think we really have addressed these A and Bs. If you agree. I mean --

DR. WALKER: Yes. I think, largely, I think the age group, we -- I'd like you to address that. And then in terms of risk management plans, you can either address it under B or later on. But I think you should discuss that.

DR. BIGBY: In what age group should etanercept be approved for use?

DR. STERN: Excuse me. Might -- with all the discussion that's gone on, might it be more efficient to first go to 11, because what we advise for A and B might well vary with what restrictions or not restrictions we put on it in terms of the indication.

DR. BIGBY: That's fine. So let us put to the vote. Is there a degree and severity of psoriasis that should be set as a minimum for study enrollment?

DR. WALKER: Yes, these questions are in general about pediatric studies for psoriasis. But you could certainly give these same responses -- you know, to 9B, under the second bullet. Particularly -- and gear them towards this product, but remembering that there are other products that will be interested in this indication.

DR. STERN: There's also a way -- I think there's been some talk both yesterday and today of mandatory registration in prospective trials. If you have to go -- in prospective surveillance studies. And if you have to go into a study to get the drug, and you have to have a certain severity to go into a study; therefore, you're really only approving it for that indication -- if there's a feeling about the need for more information from mandatory

enrollment and studies.

DR. CRAWFORD: Mr. Chair, I'd like to actually ask our ethicist her comments. Study participation is still voluntary, so I would have a little trouble with mandatory study enrollment.

DR. MAJUMDER: It's sort of core, going back to Nuremberg, that the informed consent of the subject is absolutely essential. But there have been some comprises made over time. And I'm still conflicted about this, but I know with the multiple sclerosis drug, for example, it is a mandatory registry. And I guess the idea is that it's a sort of public, community good, and you're getting the drug, but that's kind of the trade-off -- we need more information.

And also that patients generally, I mean, I can -- this is what I've heard outside this session and today -- have a very strong interest, usually, in seeing that information created.

So I know that there are people who don't even think children should be allowed to be enrolled in clinical trials because they can't give informed consent, or at least no non-therapeutic trials. I think that the -- sort of where we've moved is still a great deal of concern about coerced -- being coerced into being that human subject. But if you view it more on the public health model, then there's some justification.

I don't know if others have comments on that.

DR. BIGBY: I actually think that we should actually go back to 9B and try to answer this question. In what age group should etanercept be approved for use? The sponsor has suggested age 4 to 17. I guess a way to put this is, is that age group acceptable to the Panel?

And we can vote, make your comment about alternatives -- if it is not. So how many of you think that the proposed age

range, 4 to 17, should -- is acceptable?

Those voting yes, raise your hand.

Go ahead. What?

I'll vote yes. Those voting no,

raise your hand. And abstainers?

MS. WAPLES: One person missing?

Okay.

DR. BIGBY: Who's missing?

Can you repeat the vote? Those

voting yes, raise your hand. You're voting

yes on the age range here.

DR. O'NEIL: Age?

DR. BIGBY: Seventeen.

DR. O'NEIL: Yes.

DR. BIGBY: Those voting no, raise

your hand. And abstentions?

The tally was seven yes, zero noes,

six abstentions.

Dr. O'Neil?

DR. O'NEIL: Thank you. I think that

there's a tremendous dis-service we do to the

children of the world if we don't allow them

study as well as drug access. And I think it has been shown to be as safe as the data now allow; and we won't know more, as has been pointed out, until it reaches the open market for children with this indication.

Excuse me, I just ran.

DR. MAJUMDER: Mary Majumder. I abstained.

DR. BIGBY: Michael Bigby. I voted yes. I mean, if it is going to be used, the range seems reasonable to me.

DR. THIERS: Bruce Thiers. I abstained, because I didn't recall how many children at the lower end of their range were included in this study.

DR. LEVIN: I abstained for the same reason, although I think I remember it wasn't a very big number, so --

SPEAKER: Very few, yes.

DR. LEVIN: We didn't have much data.

DR. DAUM: I voted yes because I don't know anything about use of the drug in children

under four. And as I stated with previous votes, I think that there's sufficient data to suggest that there's benefit to a very small, select, severe group of patients 4 to 17.

DR. CRAWFORD: Stephanie Crawford. I abstained because I also recall that the elaboration of the numbers I believe from four to eight was very small. So based on the data available, I can't make a vote.

DR. DRAKE: Lynn Drake. I voted yes. I think once we've decided to recommend approval to the pediatric population, I think we should leave it to the people who are treating those children as to when they think it's appropriate to put them on the drug. Once again, I'm leaving it to the parents and the doctor and the patient to make those tough decisions about when to start.

DR. HECKBERT: Susan Heckbert. I voted yes. I think getting adequate data on the very young group is not going to happen, and we really can't require it. So I felt this was a

reasonable range.

DR. RINGEL: Eileen Ringel. I abstained. I thought the number of kids in the lower-age group in the study was small. I think the risk for those prepubescent children is increased.

And I really wish that we could vote on the moderate to severe issue so I can stop abstaining, and voting in directions that I really don't want to vote in.

DR. DAUM: I agree completely.

DR. SHWAYDER: Tor Shwayder. I voted yes. Generally, I don't like age restrictions. I like to use things whatever I think is appropriate as a physician. However, psoriasis in a kid between the ages of zero through four has no impact on their own perspective, only on the parents' perspective.

And therefore, I think -- you know, before they go to kindergarten, that's fine; we'll just do it after they go to kindergarten.

DR. BIGBY: With regard to -- we can actually add a question at the end. But the FDA doesn't want us to sort of change the questions that they've asked. This is in response to the idea of changing the indication from moderate to severe to just severe. Is this correct?

DR. WALKER: That's correct. But we do hear your comments on the issue of the indication. If anyone has more comments to make, I'd certainly like them to put them in the record.

DR. BIGBY: We'll go on to No. 10, if nobody objects. Is labeling by itself an adequate vehicle to educate physicians and patients concerning the benefits and risks of initiating a continuing treatment with etanercept in pediatric patients?

If you think that labeling is adequate, that is a yes vote. And how many are voting yes? Yes? So that's two yeses. And how many vote no? Can the yeses raise your hand again? So there's three yeses.

The tally is three yes, nine noes -- the yeses, raise your hand again. All right. Four yeses. So the tally is four yes and nine noes.

We'll start with Bob.

DR. KATZ: I assume the other educational --

DR. BIGBY: Name.

DR. KATZ: Robert Katz. I voted yes because that's how people are informed, by labeling.

And the remainder goes to information, medical education to physicians, and physicians communicating with patients.

DR. STERN: I voted no because of the extraordinary imbalance in information given about this drug to the general public. And until there is an end of direct-to-consumer advertising for adult as well as children, because parents see it as well as people in the age group -- we have to have some kind of counter-detailing and very strong information,

or we're going to have overuse of this drug where risk will outweigh benefit.

DR. O'NEIL: Kathleen O'Neil. I voted no because I want to be sure that the educational mechanisms are sufficiently strong for both prescribing physicians and for families.

DR. MAJUMDER: I'm Mary Majumder. I voted no because I believe a more-comprehensive risk management plan is warranted, and the sponsor is proposing to do more. And as I understand it, FDA has a role in reviewing those materials. And hopefully -- you know, they have some leverage to make sure that, for example, booklets that are distributed directly to patients or parents are giving a complete and balanced account that reflects sort of the discussion here.

DR. BIGBY: Michael Bigby. I voted no because I don't think labeling alone will prevent indication creep for this drug.

DR. THIERS: Bruce Thiers. I voted

yes because labeling is the traditional way we communicate benefits and risks. Although I do agree with Dr. Stern's comments about direct-to-consumer advertising.

DR. LEVIN: Arthur Levin. I voted no. One, partially, because of the generic literature that says that labeling isn't terribly effective in communicating and guiding physicians in their prescribing practices.

And two, I think -- as has been said, even the sponsor thinks this product requires a risk management program, including a medication guide, and I think the more we can do to make sure that the drug is used appropriately out there in the community.

And that patients -- I mean, labeling is very difficult to read. I don't think patients and parents are going to get much out of labeling.

So there's clearly a need for a lot more. It's necessary, but not sufficient.

DR. DAUM: I voted no, and have

nothing to add to the comments that have been made.

DR. CRAWFORD: Stephanie Crawford. No, because -- my previous comments I think made it clear, I think there needs to be a much better-defined risk management plan.

DR. DRAKE: I voted no because communications study data, and how people hear and listen to things and then follow through, you've got to tell them at least three times, in three different ways, for it to take. So I really think there needs to be a significant effort in educating.

There will be a creep, and there will be confusion about the difference between pediatrics and adults, if they're talking about generic psoriasis.

DR. HECKBERT: Susan Heckbert. I voted no, for the reasons already given.

DR. RINGEL: Eileen Ringel. I voted yes. The question is a vehicle to educate physicians and patients, not should there be any

other monitoring. So I really restricted it to that. I've noticed that once the label is made, pharmaceutical companies are more than happy to educate, and educate, and educate, because it's basically a way to advertise their drug. They almost over-educate. Sometimes I think I'd just like -- just leave me alone.

But the other thing I do think would be a good idea would be the medication guide. And so, that's the only other thing I could think of that they could really do to educate, that they're not doing.

DR. SHWAYDER: Tor Shwayder. I voted yes. Labeling should be enough. I don't want to stack on another I PLEDGE-type thing where you have to jump through a bunch of hoops to prescribe something. We're intelligent enough to read the data.

DR. BIGBY: I think there are four people who have to leave right away. The FDA would like you to go on record with your name and just some suggestion about what sort of risk

management program you would recommend.

I'm not sure the four of you that have to go. I know Robert Katz is one, so why don't you start.

DR. KATZ: I just -- on No. 11, it said, is there a degree of severity? Psoriasis should be for severe. However, the physician and patient defines that, not (inaudible) moderate. And --

DR. BIGBY: Just in terms of a comment about risk -- you know, like, what kind of risk management you would recommend for the use of etanercept in treating pediatric psoriasis.

DR. KATZ: You mean --

DR. BIGBY: Just a --

DR. KATZ: Follow-up --

DR. BIGBY: Just -- yes, a comment, yes. Like once it's approved, what would you like the company to do, or?

DR. KATZ: Very stringent post-marketing follow-up, possibly short of mandatory registration.

DR. BIGBY: So who else has to leave right away? Eileen?

DR. RINGEL: Yes. Also limit it to severe --

DR. BIGBY:: Name.

DR. RINGEL: Oh. Eileen Ringel. Limit it to severe. And I would have to be here for the discussion. I was confused, concerned, whatever, by the drug -- by the pharmaceutical company's saying that it would be extremely difficult to do a registry because there's already so many indications for it. I don't know to what extent that holds water, and so I would have to hear more about it.

So I'm going to just abstain.

DR. MAJUMDER: Mary Majumder. I don't know that I can say that much, but I do think, given what I've heard about how long it may take for additional malignancies to show up, it does need to be a real long-term study.

I don't know if this was the case where it was five years, but I think

something beyond that seems appropriate, although I'm not an expert in that area.

I just wanted to mention that severity is also a concern of mine. I think that's probably also on the record. But I actually found, in one of the sponsor presentations, the quotation from the American Academy of Dermatology Consensus Statement.

I'm not saying -- you know, put that in the label, but I thought it was very good at suggesting the different dimensions, including type and locations, severity and extent, response to previous therapies, symptoms, including pain and itching, and quality of life considerations, as the things that you would want to look at.

And I'm sure in the dermatology field, you all know that. But it just seemed to be a nice summary.

DR. BIGBY: Dr. O'Neil? Oh, okay.

DR. CRAWFORD: Thank you,

Mr. Chairman. Stephanie Crawford. I would also favor consideration of limiting it to however the clinician, prescribing clinician, defines severity -- as severe. On top of that, post-marketing commitment to study the long-term use in this population for this indication. And just reasonable reconsideration of the parameters for who would be enrolled in a safety registry.

DR. THIERS: I assume you want the people who have 2:00 vans to talk. Okay.

Bruce Thiers. I would agree with what Dr. Katz said about just follow-up of patients and -- putting together these programs is very difficult. I don't think I would go for mandatory registration. But I would put it -- I would ask the FDA to put together some kind of program where these patients -- where there is some commitment on the part of the company and the prescribing physician to follow-up on these patients.

In terms of the indication, I'm

okay with limiting it to severe as long as we make it clear that the physician and the patient together determine whether the psoriasis is severe; that there's no quantitative way of measuring it.

DR. DRAKE: I'm -- excuse me, I'm sorry.

DR. LEVIN: Excuse me.

DR. DRAKE: Mr. Chairman?

DR. LEVIN: If it's a point of information about the 2:00 van thing --

DR. DRAKE: That was what I was going to ask --

DR. LEVIN: Will the vans wait for us, as long as our flights are okay?

MS. WAPLES: Yes.

DR. LEVIN: So it's based on flight time, not van time.

MS. WAPLES: Yes.

DR. HECKBERT: So what was the answer to that question?

DR. DRAKE: Well, Mr. Chairman, my

comments are very simple. I agree with Bruce.

Lynn Drake.

DR. LEVIN: And my comments are simple. I agree with Bruce.

SPEAKER: The van's already left.

SPEAKER: They're going to be fine.

SPEAKER: Okay, fine. Thank you.

DR. BIGBY: Dr. Stern.

DR. STERN: I'm sorry. I didn't mean to have it on.

DR. BIGBY: Oh --

DR. STERN: I think that the clinically and regulatory way to approach this is to approve it for severe, and to have, as we talked about yesterday, mandatory registration in a long-term safety study so we can see what happens to these individuals.

As I talked about yesterday, this is another -- this one, we know about. This is a $15,000 a year drug. This is substantial resources.

It's not like putting someone in a

study of a drug that does not require substantial social resources that does not have likely substantial risk, and that it's not worth taking the extra time to enroll someone in a study if you're going to put them on that in this age group.

So I think this only works as an approval if the sponsor can come up with a robust plan for making sure that every child treated for psoriasis, we know about, and we can get some follow-up information on them, at least for as long as they're on therapy.

DR. O'NEIL: Kathleen O'Neil. And, unfortunately, they couldn't put me on a plane until tomorrow. So if anybody needs to talk before me, that's cool.

I basically agree with what the discussion has been all along, which is that the more-severe form of psoriasis is where we should start with the labeling.

I also think that the post-marketing plan, as described scantily in

the information we got, looks appropriate. And I guess the real answer is that the devil is in the details. I am not certain that it's going to be entirely feasible to do mandatory post-marketing surveillance, but I'm sure that the FDA can figure that one out.

DR. DAUM: I'm also in the 2:00 van, weighing in. I strongly favor the severe option, if there is an option. The other thing is -- and maybe Lisa or some other --

DR. BIGBY: Name.

DR. DAUM: I'm sorry. I can't learn it. Robert Daum is my name.

Maybe Lisa or someone else from the Agency could help me, but there are some things in the Pediatric Advisory Committee that we've sort of starred for that the Committee wants to see this again.

And I wonder if this isn't one of those things, where either this Committee or the Pediatric Advisory Committee, or both,

have a built-in mechanism to get updates on this issue, since we have these safety concerns.

DR. MATHIS: I will address that, actually. Because this was done in response to Pediatric Research Equity Act required study, then it will be followed up at the Pediatric Advisory Committee one year after labeling, regardless of outcome of study. So if the drug gets labeled for use in the pediatric population, it will have an annual review, at least one annual review, with the Pediatric Advisory Committee.

More reviews upon your request.

DR. DAUM: We would see the AERS reports, for example, of that, and hear the progress in enrolling in the safety study --

DR. MATHIS: I would anticipate that would be the case.

DR. DRAKE: I know it'll go to the Pediatric Committee, but I think, since dermatologists will be probably the primary

prescribers in this arena, I'd like to request that the FDA also include some dermatologists when that comes before the Pediatric Committee, just to make sure we're educated, too.

DR. WALKER: I think you make a good point, and we will absolutely keep the Dermatology, the DODAC, apprised.

DR. HECKBERT: Just to go ahead and give my vote. I'm Susan Heckbert, and I would vote that in any additional studies that might be done, which is what 11 seems to be, that psoriasis -- the people enrolled -- the children enrolled should have severe psoriasis.

Also, I think that if this drug is to be approved, the label should be for severe pediatric psoriasis, not moderate or severe.

And then finally, I agree with Dr. Stern's suggestions regarding mandatory registry of pediatric patients who receive this drug, although I would appreciate some discussion, if we have time, about this idea

that since the drug is already available, that there would be some way of skirting around this, and what the concerns are regarding that.

DR. SHWAYDER: I agree with all that. Nothing new to add.

MS. REESE: Excuse me, Dr. Bigby. May I make a comment?

We would ask any members whose flights are not before 4:00 p.m. to please stay at the table. The FDA will need your comment. We'll need you to stay. Thank you.

DR. BIGBY: Michael Bigby, and what I would say about this is that I heartily agree with Dr. Stern about the difficulty in sort of having a distinction between direct advertising to adults not having an effect on children. And that the labeling is not going to be adequate. I think if you're going to release this to children, you need to re-address the issue of direct advertising to adults.

And I don't think that you're going

to get mandatory registration. And I think that the post-marketing surveillance is going to be inadequate.

A question for Susan. Do you really want us to discuss study design for psoriasis trials in general?

DR. WALKER: Eleven, twelve, and thirteen, if you have any brief comments at this time, this is a chance to hear from the Committee. But I'm sure we'll have wider discussions on this topic going forward.

So I think we've really learned a lot from the Committee, and really appreciate the advice and comments we have received today. And I think it's been a really excellent discussion.

DR. BIGBY:: So does anybody have burning comments about study design?

DR. HECKBERT: I just have a -- it isn't about study design, it's about the direct-to-consumer issue. I would second the comment that if this drug is going to be

marketed to children, that there should be a real consideration about whether direct-to-consumer advertising to the general population -- that is, for the adult indication, is appropriate. So I'm not sure that it is.

DR. BIGBY: I have a note here saying -- we can't do Dr. Katz -- but I have a note here saying that we did not get Dr. Stern to go on the record about 9B, the age.

You know, the --

DR. STERN: I believe I voted -- I believe I abstained, because I thought that, as I recalled, the data in the younger age groups was so sparse that I really couldn't say anything. But I think if it is going to be approved, we have to do it for the entire age group that has been studied. But it's really very sparse data.

DR. BIGBY: So at that, I think we will conclude our deliberations.

Thank you all very much.

DR. DRAKE: Michael, I just wanted to

add that I think -- I wanted to compliment you as the Chairman. You did a really good job the last two days. These have been some really thorny issues, very difficult discussions, and I just wanted to compliment you because I thought you did a good job.

DR. BIGBY: I appreciate it.

DR. DRAKE: I want to thank the FDA for giving us good prep. I mean, you guys really came through with a lot of good stuff.

As did the sponsors, frankly. It was a beautiful meeting.

(Whereupon, at approximately 2:19 p.m., the MEETING was adjourned.)

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