event that occurs.

DR. DRAKE: Dr. Adelman, we actually--I think the whole committee appreciates that you are doing that. We also appreciate that you have done a valiant effort to give us the information we need.

What I am hearing around the table though, and I must really restrict this in the future to the committee, please, I want to ask the sponsor not to come to the microphone. If a committee member wants to address a specific question to the sponsor, you have my absolute permission to do so, but we must allow the committee time for their deliberation without a point-counterpoint at every turn because much of this will fall out in the discussion.

I have chaired many of these committees. You would be amazed at how much falls out during the discussion of intelligent people sitting around the table thinking about it.

So I would like to continue, please, with the committee deliberations. Dr. Tan?

DR. TAN: I was going to point out the data just presented, I think, the follow-up data is biased. I think the patients who don't respond,

you are not going to give him alefacept again; right?

DR. DRAKE: A little slower.

DR. STEVENS: He said the study is biased because the people who don't respond are not given further rounds of alefacept.

DR. TAN: If the patients don't respond, they won't get this drug again. So, therefore, if you follow up those patients, you are always studying those patients who respond. But, when you first give the drug, the biologics, to the patients, you don't know whether that patient is going to respond or not.

DR. DRAKE: That's right. There are no predictors. Absolutely. That is a very good point. Thank you.

DR. EPPS: One-tenth of people were at the fifth course than started out, 1,300 in the beginning, 116 were at the end. So there was quite a bit of drop off for whatever reasons. We don't really know.

DR. DRAKE: Other comments? Bob?

DR. SWERLICK: I don't think you can interpret that data necessarily that way. Those people were staggered in how long they had been on

it. So some may not have been on the drug long enough to be through the fifth course. Some may have responded and stayed clear.

DR. EPPS: But that's what we don't know, how many cleared.

DR. SWERLICK: But I think that is a separate issue. You are talking about efficacy versus safety issue.

DR. EPPS: That is an important issue.

DR. SWERLICK: In terms of the number of patients who have undergone the fifth course, it comes back to the same question I asked earlier. If we are going to set a standard, a higher standard, is it going to be an eternally moving one. What I am trying to figure out is how many patients would we have to study in order to detect a certain frequency of adverse events and how many patients would need to be studied.

So, if this isn't enough, how many patients would be enough? I don't have the statistical background to answer that, but are we talking about another 1,500 patients? Are we talking about 15,000 patients? How many is that?

DR. DRAKE: Dr. Seigel?

DR. SEIGEL: It depends on what you are

looking for, but if something doesn't occur in the background and then you study 150 people and you don't see it, you can be pretty sure that the rate is 2 percent or less from a statistical perspective.

If you increase that to a thousand people, you can be pretty sure that it is a quarter of a percent. So it is going to change. If it has a background occurrence, as serious adverse events go, as I said, it may be hard to tell no matter how many you study whether it is real.

DR. SWERLICK: Because I have the same anxiety regarding this whole new class of medications, but if our response to that is simply to say, well, we need to study more, we need to study more, again, it comes back to how much is enough. It has to be reasonably defined.

DR. DRAKE: Dr. Abel and then Dr. Tan.

DR. ABEL: Why couldn't we vote to approve it with some limitations and not feel that it may be--

DR. DRAKE: It is certainly one of the committee's prerogatives.

DR. ABEL: Because cyclosporine was approved for one year. Maybe there are some

thoughts about multiple cycles within a certain time period and it could be approved with qualifications.

DR. DRAKE: The committee can make any recommendation they want to to the agency. We are free to make a recommendation of--here are your options. You can turn the whole thing down and recommend that it not be approved. We are not the final deciding authority, you should know. We are just an advisory body to the FDA. They will make the decision.

But we can recommend based upon our deliberations that it shouldn't be approved at all. You can recommend that it be approved but with some caveats; here is what we think you ought to continue to look at. Or you can say, boy, we think it is great. Let's go. You have a range and that is what we are here for.

We are to give the agency advice. They will make the final determination based upon what they have heard from the sponsor, from our experts and from you guys. So your role here is to help advise the FDA staff on what they might want to look for irrespective of what our recommendation is because they do not have to abide by our

recommendation.

But we certainly can make lots of them. We have a lot of fun.

DR. SEIGEL: We will appreciate all of them. Thank you.

DR. TAN: I had one more. I think this has been brought up several times. I think, in terms of the incidence rate, probably you want to consider this in terms of the adverse events for the alternative therapy as well.

DR. DRAKE: Okay. I am going to make kind of a summary statement here. Would you all agree that if we look at Part C under malignancies, it says they went from 0.5 in placebo to 1.1 for treated patients. I think the very same set of questions could be asked about malignancies that we have just asked about the rest of this section.

Is it fair for me to say that we want to translate almost all of our comments from A and B to C? The very same questions about malignancy are going to apply. Yes?

DR. MORISON: With one proviso, that infections will crop up probably early. Malignancies may crop up late. So you could be two years into a course of therapy and then start

seeing malignancies.

DR. DRAKE: I agree with you totally. We need to have a longer time line for monitoring for malignancies.

DR. MORISON: To go to the extreme, you might say, well, you have got to look at these people for fifteen years before you start finding melanomas.

DR. DRAKE: Look at PUVA. Two years was the earliest.

DR. MORISON: Two-and-a-half years.

DR. DRAKE: Two-and-a-half years was the earliest; yes. So you will need a time line on malignancies because they just are slower. No matter what we do with it, you need a longer monitoring period for that.

I must admit, I still am a little concerned. The safety data that we just heard on the animals bothers me just a little bit. I really think that hyperplasia of the B-cells really must be monitored to see what--it could just be reactive, but it also needs to be in the monitoring portfolio to make sure that that doesn't signal anything important.

Now, then, Dr. Weiss and Dr. Seigel, do

you have enough information on Roman numeral I or what other questions would you like to pose to us or ask the committee?

DR. WEISS: I think you have addressed those as well as anybody could.

DR. DRAKE: Yes; it is a little hard. But we are getting there. At least we are pulling out some information. As far as I am concerned, III and IV sort of go together because the first question on IV is how safe and effective is it.

So I want to devote just a couple of minutes to efficacy. I want to talk about efficacy for just a moment and then we will do IV because I want to make sure we get that out of the way before--the question on III, on efficacy outcomes, because I think this is a quick for us, on the outcomes part, the question is--we are back to PASI. Is it okay to suggest that perhaps we have discussed PASI already? Can we dispose of that first question? Don't you have enough information on opinion on PASI?

DR. WEISS: Yes; that's fine. It is really more the issue about have they shown it to be effective and then the overall risk-benefit integration.

DR. SEIGEL: I would simply add, however, that the question, although asked about in the evaluation of this product and I think we have heard well about the use of this in the evaluation of this product probably has implications for what sponsors seek to show for a variety of other products that come along in psoriasis.

So, to the extent that there might be suggestions, as some have said, that the PASI 75 is insensitive or too high a response rate for trials, I think, in the interest of time and getting today's job done, it would be okay to skip over that.

But, if we don't come back to it, we might, at some future point, want to discuss with this committee what are the optimal endpoints given what we know now for new psoriasis trials.

DR. DRAKE: I couldn't agree with you more. I think that we have grappled with this issue on two separate committee meetings already and I think it wouldn't hurt to have a third one because we have got all kinds of stuff in the pipeline that this committee and the agency are going to consider.

So the more well-defined we can get is

going to help the sponsors. It is going to help the committee. It is going to help you. So, Dr. Seigel, I totally agree with you. I think that is an extraordinarily important comment. The bar of 75 percent I think is reasonably high. On the other hand, I bet you if we had some other slides, we could show some other folks who didn't improve as much.

I think you need to see the whole spectrum as you are making these decisions is what I am trying to say. You need to see some of the placebo patients to get a sense. You need to see the whole spectrum if you are going to be making determinations about the PASI score, I think.

Let's talk about efficacy. Let's have just a little bit of open discussion about efficacy before we actually go to the vote because we haven't discussed that. I want comment from the members of this committee about efficacy of this, whether you use the PASI score, the physician's global assessment, whatever you use. What are your reactions regarding the data and the information we have received.

Dr. Abel?

DR. ABEL: I think you have to look at all

three assessments, PASI, physician's global assessment and the quality of life. I think that the efficacy seems very impressive especially in terms of the fact that you think of this as a remittive therapy and that there are going to be long remissions and we don't have any treatments for psoriasis that are like that except for PUVA, and maybe UVB.

So I think it definitely has plus.

DR. DRAKE: Dick?

DR. TAYLOR: I agree. I am impressed with the efficacy of this product. I think, in looking at the patients that we have seen and hearing from patients that have received it, I agree that looking at all three of the parameters for evaluating efficacy, that they are all good. As I said before, I think the PASI 75 is much too high and PASI 50 would probably be more reasonable.

If you did that, then the efficacy is very impressive.

DR. DRAKE: As a custom I have, I like to go around the room and make sure everybody talks when we get to this point because I want to hear what everybody has to say about both efficacy and additional comments on safety.

Bob, would you start. Dick, you can repeat what you have or not, but everybody in the room be thinking about what you want to say because I am going to call on everybody.

DR. SWERLICK: My impression is that when compared to what I use now, this drug seems like it will be as effective or more effective and potentially even safer than some of the other poisons that I have to resort to using.

I had one other issue to raise.

DR. DRAKE: Please.

DR. SWERLICK: That has to do with the safety. This is likely to be combined with other biologics. That actually hasn't come up yet. Should we wait until--that has to do with the product labeling or--

DR. DRAKE: Yes; let's wait on that. But using it in conjunction with something else is a problem no matter what we approve, or don't approve. It is just absolutely an issue. But, for now, I would like to keep it sterile. Let's assume this is a sterile process.

I don't know if I am going to invite you again or not because you ask too hard questions. I'm just teasing, you understand. They are very

important. Do you want to comment on safety while you are at it?

DR. SWERLICK: Again, I think that it is not if something happens to somebody on this drug. It is when. But I think, compared to the risks associated with everyday life that this compares well with other therapies given the information we have on hand now, and that the amount of additional study that would be required to identify the low-frequency catastrophic events, the 747 going down in New York City sort of business.

The numbers involved in that sort of study would be huge you will pick it up in postmarketing. That is my bias.

DR. DRAKE: Dr. Taylor, please give us your total range of thoughts.

DR. TAYLOR: As I said before, I think this is a sufficiently efficacious agent to consider approval. I would agree that, compared to other treatments that I presently use all the time, this is at least equal if not better than most.

I think the other issue is that, as far as the risk is concerned, I think many of the problems that we have all identified will be identified in a registry if the registry is set up well enough and

it will be identified much more rapidly postmarketing than it will be premarketing. So I would think that we are not going to get the numbers premarketing that we need to make the decisions. So I would think that we know enough about the risk right now to go ahead.

DR. DRAKE: Dr. Abel.

DR. ABEL: I would agree with that. I think it should be approved now. I think it compares favorably, more than favorably, with other systemic therapies for psoriasis. I, too, am concerned about the risks and the repeated courses, the number of cycles, the time interval. I think that we have to develop guidelines to decrease the risk of potential side effects and monitor these patients very closely long-term for both short-term infections and long-term for infections and malignancies. And there may be some caveats written into the approval.

DR. DRAKE: I am going to derail my own process here. I wanted to ask everybody a quick opinion about dose. Without it being a total discussion, I forgot we didn't address that. I am going to go back to you three and ask you to give me your opinion on dose and then would the rest of

you include that as we go around the table.

Bob, tell me what you think about dose.

DR. SWERLICK: I am confused. The pharmacokinetics would suggest that the dose is not going to be critical, but there is enough data that would suggest that there may need to be dose adjustment for certain subgroups of individuals based upon size, not necessarily just weight but other factors.

I think, again, it is one of those things that it can be hashed out post-approval.

DR. DRAKE: Do you recommend further studies on that?

DR. SWERLICK: Yes.

DR. DRAKE: Dr. Taylor

DR. TAYLOR: I have already given you my impression of dose earlier on. I really think it ought to be weight-adjusted rather than a given dose.

DR. DRAKE: Dr. Abel?

DR. ABEL: That makes sense to me. We talked about that early on and I would favor the weight-based. But that doesn't seem to apply with IM, so if it were just IM, it seems to be okay to use the fixed dose. I am wondering about the

options for IM versus IV. How are we to choose? Why are both of these routes being offered?

If it is just the fixed dose, then maybe IM is the ideal way for it to be given.

DR. DRAKE: Thank you. Now, Ms. Knudson, we certainly haven't heard much from you today. As an IRB person, you probably have quite a few comments on safety and everything else. So please share them.

MS. KNUDSON: My concern, of course, is that this is a highly vulnerable population. I suspect that as soon as it is approved, there will be many, many, many patients who will want to take the drug and could be followed. So long-term effects I think could be found with some ease as long as that registry is set up appropriately.

I think the safety is certainly better than toxins that are used currently. This is infinitely better. It seems to be at least as efficacious. I don't think I can comment on the dose except I am concerned about children and size and if children are going to be included.

DR. DRAKE: Thank you. Dr. Stevens?

DR. STEVENS: With respect to dose, I think we have heard the issues with respect to

weight and all of that. The other side of that observation, of course, is that if you think that it is less effective in heavier people, then the data would shake out that it would be more effective then we are thinking globally for the lighter people when we look at the entire cohort that was studied. So I think that is a postmarketing issue.

My remaining question with respect to dosing goes back to what I mentioned earlier about the reduction of lymphocytes at six weeks. I think you can always redesign experiments and studies. There are infinite variations that you can do on these. My question, with respect to dosing, is the twelve-week dosing regimen as opposed to a shorter one. But, again, I think that is one for postmarketing.

I am also impressed with efficacy, as everyone else has mentioned and I agree with the comment that was made explicitly by Dr. Tan but reiterated by the others that the question before us with respect to safety goes towards if we do not allow this therapy to be available, what will these patients be doing otherwise.

They will be using these other therapies

that have been demonstrated to have safety issues.

DR. DRAKE: Dr. Katz.

DR. KATZ: As far as using other therapies with safety issues, no doubt this therapy will have safety issues also but that would have to be acceptable. As far as safety, thus far, probably the safety profile is fairly good. There are some indications, though, that there may be problems. I feel that there is not enough people who have been treated with these indications, with infection and malignancy, that we have to be much more cautious.

Also, as far as efficacy, there is no question is it very impressively efficacious in a small number of patients. Now, there are people here who treat more psoriatics than I do, although I have my average patient share. But some people have psoriasis clinics and so they know more than I do.

So when they say it is as efficacious as anything, then I respect that. However, with a PASI even of 50 which we will say is good, 24 percent over placebo--24 percent. Now I ask those who said it is as efficacious as the others, do you not get more than 24 percent improvement with PUVA, with methotrexate, 80 percent, 80 percent with

PUVA. Of course, I am talking with Dr. Morison here so he can address that.

Those have their risks over decades. As physicians, we have to make that judgment with our patients whether they are willing to subject themselves to those risks. But I think that it would be a useful alternative after more studies are done but, certainly, clear or almost clear 9 percent over placebo, and 16 percent PASI 75 certainly shows that it is efficacious, but I wouldn't agree with its being impressive.

The other thing that bothers me a little and I would admit that this may be irrelevant, especially with respect to what Mark said and he couldn't differentiate it. But I wonder about the blind being negated in part so that, really, the efficacy is even really less than we are told here because the same physicians are--I mean, there was a difference in I think it was 11 percent it the IM reaction. So I have my reservations.

DR. DRAKE: Thank you, Dr. Katz. Dr. Morison?

DR. MORISON: In addressing the three issues, I think as far as weight is concerned, everything I have heard today sounds confusing to

me. It makes sense to me that a milligram per kilogram approach would be the best approach but hearing all the data, I am confused as to whether that is going to be possible to sort out with further studies. Certainly, to me, it would be an ideal approach.

So far as the PASI 75 is concerned, I sort of take exception to the comments that have been made to some extent. Let's say I am in a different camp. I am used to dealing with narrow-band UVB and Hoover's main treatments and they certainly do exceed PASI 75. Hoover, you can clear people to 95 percent in a very consistent way.

I think you can clear 90 percent of patients with PUVA and UVB to 95 percent clear. So, certainly, those treatments have a higher standard.

Having said that, I would 100 percent agree with everybody's comments that we need more agents because certainly I have patients who are in trouble, end stage, can't get in for treatment and I would love some more agents to use to treat psoriasis because certainly the ones we have now, methotrexate and Soriatane, and cyclosporine have lots of drawbacks.

The final point is my only real concern is safety. I think we are sort of launching into a biologic experiment where I am not quite sure we are headed. When I say that is the one concern I have is malignancy because the psoriasis population is a unique population, quite different from rheumatoid arthritis patients and such like.

This is a group of patients who spend a maximal amount of time down at Ocean City. They have had a maximal exposure to UVB and many of them had a lot of exposure to PUVA. They are all primed for the development of skin cancer. Almost the whole severe group of patients with psoriasis are primed to develop skin cancer. It is something that is going to take a few years to develop.

We have already seen it with cyclosporine. I hope we don't see it with this particular agent. That is why I think that we need a very solid follow up to detect it as early as possible.

DR. DRAKE: Thank you, Dr. Morison. Dr. Epps?

DR. EPPS: Thank you. I think I have made some of my impressions known. Of course, we all wish we had more agents to use. I would have hoped that statistically and otherwise it would be

stronger in support of this medication even though I do tend to think beyond just the nine months of improvement. Even a twenty-year-old could have a life-expectancy of fifty more years. And we just don't know.

Of course, we are not going to wait fifty years, but my point is that even if, in this brief period, there was malignancy potential, I think we need to think very seriously about it even as Dr. Morison has already alluded to, PUVA exposure, UVB exposure and also natural-light exposure.

The other signal is infection. Sometimes, it is not the opportunists that we see. It is the severe common infection. It is the ones that we see all the time which are more severe or act differently that we need to watch for.

Should we get to the dosing, perhaps a body-mass index may be a better way to look at it rather than just kilos. There have certainly been a lot of things in the media recently about overweight of Americans and other ways to look at that, but BMI may be one way of dose as opposed to just straight kilograms.

DR. DRAKE: Dr. Epps, thank you. Dr. King?

DR. KING: I am struck by the three different ways of measuring effectiveness but my mother was a business woman and she always said that, "You may have it, but the customer may not buy it." So PASI always reminded me that the physician and the patient were looking at the same thing. You could agree on how much you have. The physician global was what the doctor thought was there, but the quality of life is what the patient perceives.

So I have always put more emphasis on how much did the person perceive that I had done for them, how much did their psoriasis improve. Sometimes, people go away happy with, say, 50 percent or even a small patch that was on her face and yet they could cover up the rest of it.

So I am struck that this is efficacious. It may not be the total body cure, but there are lots of folks who have not only no access to a psoriasis daycare center, they have no access to a dermatologist.

So I come down on the side of a unit dose and access where people can inject themselves under the supervision of the dermatologist, et cetera, so they don't have to figure it out. They are not

going to give themselves IV this drug or any other drug. Having taken insulin shots, myself, I will tell you I would much rather have a fixed dose than trying to calculate what I was supposed to take.

So I come down on the side this is efficacious as a nice alternative. It doesn't interfere with the liver or kidney and you have a certain population of patients that just can't take these. So, for a home-therapy unit dose, efficacious may be not the barn burner, then I come down on the side of approval of this drug with appropriate monitoring. I would worry lots about, as I counted in this recent review on biological therapy for psoriasis, there are already twelve agents in the pipeline so you we have to be careful what we say for the first agent like this in this category that we don't give either the FDA or the manufacturers unreasonable expectations and too high a bar so that it won't become available to patients.

DR. DRAKE: Thank you, Dr. King. Dr. Tan?

DR. TAN: I do consider that the agent is efficacious with impressive duration of remission. But I don't think there is sufficient data to suggest whether it should adjust for the weight

level, whether or not it needs to be further studied.

DR. DRAKE: Thank you. Dr. Raimer.

DR. RAIMER: As has been brought out by several individuals, we certainly do need more treatment options for psoriasis. Fortunately, most of the ones we have, their side effects don't occur until we have given them several months of treatment. So I would sort of really like having this as another option to rotate people onto as another treatment.

Obviously, all of us have patients who are sort of out of options. They can no longer take methotrexate. They don't respond to other drugs and we do need another drug to be able to treat these severe patients who are out of options.

My main concern also is with the potential of malignancy eventually developing. I am not as worried about skin cancers even though that is not insignificant because we can watch the skin. If we follow these patients closely, we can remove these lesions when they are small before they are a problem.

I think internal malignancy is more of a worry, but these are probably not going to show up

for years, maybe. So I would be in favor of doing postmarketing studies to watch for malignancies rather than holding the drug up at this point in time.

Finally, I would be for a standardized test also with more studies looking at patients on the heavy and light end, maybe looking to see if doses need to be adjusted for those patients. Some more studies for heavy and light folks, but I would be in favor of a standardized for the majority of folks.

DR. DRAKE: Terrific. I am ready to call for a vote on Question Roman numeral IV if Dr. Seigel and Dr. Weiss have no objection. Is there anything else you want me to get on the table before I call for a vote? It is okay?

Dr. Swerlick, we are sorry. You have been so helpful but you can't vote. What I would like is to vote--I think I will put them together because, if we recommend approval, the safety and effectiveness go together. That is the FDA's primary mission, is it safe and effective. So we are going to put them together.

I would like a show of hands from voting members on--oh; we have to do each one? Okay,

fine. We are going to go around the table with a vote. This question that you are voting on is has the sponsor shown that this biologic is safe and effective for use in adults for chronic plaque psoriasis.

DR. KING: Wait, wait, wait. You didn't address the issue of candidates for or there is something--they failed out of methotrexate, whatever. You are just saying naive patients who have never been treated with anything else.

DR. WEISS: I guess the first question is do people believe it should be recommended for an approval and then we can get to potentially what population.

DR. DRAKE: Lloyd, what I thought we were going to is--

DR. KING: I was just bringing that question up.

DR. DRAKE: Once we get to that, then we are going to--actually, I am going to have you go to that and to children and to other populations and to labeling; all right.

DR. KING: Right.

DR. DRAKE: But is everybody clear on the vote? Please identify your name and your vote

DR. TAYLOR: Richard Taylor. I vote positive for approval.

DR. ABEL: Elizabeth Abel. I vote yes, for approval.

MS. KNUDSON: Paula Knudson. I vote yes, for approval.

DR. STEVENS: Seth Stevens. I vote for approval.

DR. KATZ: Robert Katz. I vote for nonapproval at this time.

DR. MORISON: Warwick Morison. I vote for approval.

DR. EPPS: Roselyn Epps. I vote against approval at this time.

DR. KING: Lloyd King. I vote for approval at this time with the appropriate registry and directed by the FDA.

DR. TAN: Ming Tan. Vote for approval with caution on the second course.

DR. RAIMER: Sharon Raimer. I vote for approval.

DR. DRAKE: The Chair records a vote of eight for and two opposed. Is that correct? Does everybody agree?

DR. SEIGEL: I would just like to point

out--because we have a lot of confusion on and during and after these advisory committees. What we ask for is a vote as to whether this is safe and effective in terms of meeting the clinical standards for approval.

DR. DRAKE: I stand corrected.

DR. SEIGEL: I assume that is the vote we received and that's fine. The only reason I highlight that is because, as was mentioned and is not a subject for discussion, there are issues regarding the manufacturing this product and making sure it meets other standards that are not on the table now that we are not putting forward right now to this committee.

So I take those votes for approval as indicating that, with regard to safety and efficacy, it meets appropriate standards for approval.

DR. DRAKE: I totally--I misstated that although I thought I had covered--I did cover it earlier but I should have restated it. We are not approving or disapproving. We are giving our recommendation to further the approval process to the FDA, that we think this would be a nice drug to get on the market with certain follow up,

registries, et cetera. That is the vote of the committee.

DR. SEIGEL: Right.

DR. DRAKE: And that is reflected eight to two. Fair enough? As the Chair, I didn't vote. I tend to vote when it is a tie. And one abstention. I try to remain neutral so that I facilitate and don't bias. So I try very hard not to bias the committee.

I want to tell you that I apologize. I have got to leave. I have a mom that is ill and I just can't not get home tonight so I apologize most sincerely to the committee. But Dr. King has very graciously agreed to take over with respect to the following comments and questions.

I want to compliment the sponsor and the agency and the committee because we have accomplished a yeoman's job in a fairly finite period of time. So thank you for your cooperation with my kind of rules here but it is the only way we can get through some of this stuff rapidly. Thank you very much.

Dr. King?

DR. KING: I would like for the FDA to tell us the remaining questions they want guided

and so on so that it refocuses the committee at this point. We have now voted in favor of the efficacy provided all the other parameters that the FDA considers such as straight manufacturing, et cetera, are met.

The issues to me have to do with the product labeling. Is that the issue you want to deal with next?

DR. WEISS: Yes.

DR. KING: We will start around. Dr. Swerlick, you can't vote but you can sure talk. So jump in.

DR. SWERLICK: What are we specifically talking about at this point?

DR. KING: Product labeling, number V. What would we want on the label to say that this becomes an approved product. We have to issue a product label saying this is how we would like for it to be used and what group, et cetera.

DR. WEISS: Eventually, we would specifically like V(1) addressed.

DR. KING: So Roman numeral V, product label, No. 1; should the indicated patient population be limited to people who have failed or had an inadequate response to phototherapy or

systemic therapy rather than candidates for candidates for such as other therapies, which is why I said when we did V(1) candidates for.

DR. SWERLICK: The drug was not limited to this population in terms of its--

DR. SEIGEL: The studies were for patients who were candidates for. Some, as you saw data broken down in some cases, by those who had had prior therapy and those who had not. Sometimes, based on a risk-benefit or unknown risk or whatever, we approve drugs as second-line therapies within a class and sometimes not.

So Question 1 in this section is getting at whether the indication should be as the studies were, the broad population of the studies' candidates, or whether it should be those who have failed or had inadequate response perhaps to other alternatives available.

DR. SWERLICK: I don't see any particular reason to limit it to a population, or deny a population that was actually--it was tested on which is they are candidates for other therapies, it should be an option for patients to elect not to take cyclosporine or methotrexate or not to be exposed to UV light therapy if they feel as though

that represents a higher risk.

DR. KING: Dr. Taylor.

DR. TAYLOR: I agree. I don't think it should be limited to previous treatments.

DR. KING: Dr. Abel?

DR. ABEL: I agree. I think it should be open, open indication, because there are problems with other treatments. Patients might not be able to go a PUVA center. They might not be able to take methotrexate because they have liver disease. Pregnancy issues; we haven't talked about that whether or not there is a contraindication. But, certainly, they can't take retinoids or all of the others if they are pregnant. So I would not limit it.

DR. KING: Ms. Knudson?

MS. KNUDSON: I agree. I would not limit it, either.

DR. KING: Dr. Stevens?

DR. STEVENS: Yes; I agree. I would not limit it and I would also add the thought that one of our concerns about cutaneous malignancies--it may be, in fact, that phototherapy followed by this product may not be the optimal way to treatment psoriasis patients. So I would just add that as

another reason not to limit it to phototherapy failures.

DR. KING: Dr. Katz?

DR. KATZ: Once it is available, I see no reason to limit it. People of less severe psoriasis will limit it, themselves.

DR. KING: Dr. Morison?

DR. MORISON: I agree.

DR. KING: Dr. Epps?

DR. EPPS: I agree. Dr. Tan?

DR. TAN: It should be the same population the study was, so it is not limited.

DR. RAIMER: I agree.

DR. KING: I think that is pretty clear for the FDA. Do you want us to vote on that, too?

DR. SEIGEL: No; that's fine.

DR. WEISS: Could I just ask another question a little bit along these lines. I guess there are a lot unknowns. Dr. Stevens, you already mentioned maybe that giving this following PUVA is not necessarily ideal. Are there any specific concerns that maybe should be addressed perhaps in postmarketing of using this following certain types of other therapies, any potential concerns about accelerating the rate of either malignancies or

some other types of immunological effects that might have some clinical consequences that we should be particularly cognizant of?

DR. KING: I would open it up to anyone on the panel.

DR. STEVENS: I would just say the phototherapy. I would say that--and I also have to leave in a moment--I would just say that we do have to monitor these effects. It is a new type of therapy and I think, in the registry, which I think needs to be fairly rigorous, prior therapies and durations and responses need to be followed with the eventual analysis towards trying to identify people at low and high risk of adverse events.

DR. KING: Dr. Abel?

DR. ABEL: I agree that special caution should be taken in those patients at high risk for malignancies including those who have had PUVA therapy and cyclosporine, in particular.

DR. KING: Dr. Morison?

DR. MORISON: As far as cyclosporine is concerned, we are already forewarned because we had the transmit group and we had that they had problems in terms of developing skin cancer. So we knew that cyclosporine was not going to be a smart

idea with PUVA and it is just a matter of collecting data.

Really, it is only extrapolating from that observation that you are concerned in this particular situation. So I don't think you should say it shouldn't be used. I think we have got to get some data.

DR. KING: Dr. Katz?

DR. KATZ: I don't think that it should be restricted.

DR. KING: Dr. Epps? The FDA is asking for should we restrict it? Are there any kinds of information, the prior treatments, and so forth? How do you address the issue of what we are going to tell them, the patients, the special populations.

DR. EPPS: Certainly, there will be special populations, and they estimate that it is as many as 1.5 million people with moderate to severe. Obviously, a lot of them would have had treatments and that is quite a bit of monitoring on the FDA's part, especially if there is a registry. So, good luck.

DR. KING: Dr. Tan or Dr. Raimer?

DR. TAN: I think it should be restricted

to moderate or severe.

DR. KING: Actually, we have leaped ahead to the moderate to severe. I am not sure we have covered exactly what you want to know, but the answer is not really.

DR. WEISS: Okay. Thank you. That's good.

DR. KING: We will go back around to the should it be restricted to moderate and severe which ought to be real quick, I think, going around the block here.

DR. SWERLICK: Yes.

DR. TAYLOR: No.

DR. ABEL: Yes, as with any other systemic therapy.

MS. KNUDSON: Yes.

DR. KATZ: I don't think that it should be labeled that way. I don't think people with one patch of psoriasis are going to want to go on weekly shots, so that will limit it.

DR. KING: But that is a difference. It will be the doctor reading the PDR.

DR. KATZ: That's correct.

DR. KING: Dr. Morison?

DR. MORISON: It should be limited to

moderate to severe psoriasis.

DR. EPPS: Limited.

DR. TAN: What was just said.

DR. RAIMER: I think it should be labeled that way, actually.

DR. KING: What other issues do we have here left? No. 3; please discuss recommendations that should be included in the label regarding lymphocyte monitoring and subsequent dosing. Specifically, should the label state that lymphocyte counts and CD4 counts be followed for all subjects as was performed in the clinical studies.

DR. SWERLICK: Yes. I think it basically should be handled the same way. These are commercially available and have the same stopping rules, essentially the same guidelines, that if the CD4 count drops below 250, you hold the dose.

DR. KING: Dr. Taylor?

DR. TAYLOR: I agree.

DR. KING: Dr. Abel?

DR. ABEL: Yes; I would agree. And then, if it hasn't recovered, no repeat course should be given.

DR. KING: Ms. Knudson?

MS. KNUDSON: I absolutely agree.
DR. KING: Dr. Katz?
DR. KATZ: Yes.
DR. KING: Dr. Morison?
DR. MORISON: Yes.
DR. KING: Dr. Epps?
DR. EPPS: Yes.
DR. KING: Dr. Tan?
DR. TAN: Yes.
DR. KING: Dr. Raimer?
DR. RAIMER: Yes.
DR. KING: No. 4, please comment on the types of information to include in the warnings regarding the risks of infection and malignancy. We have beat this pretty well, so what would you like finally to say, Dr. Swerlick?
DR. SWERLICK: I would say put on the label there is a theoretical concern and that patients should be followed closely for the development of infections or malignancies.
DR. KING: Dr. Taylor
DR. TAYLOR: That seems reasonable.
DR. KING: Dr. Abel?
DR. ABEL: You might also include the geriatric patients or patients with concomitant

medical illnesses who might be immunosuppressed.

DR. KING: Ms. Knudson?

MS. KNUDSON: I agree; yes.

DR. KING: Dr. Katz?

DR. KATZ: I agree to include that caution.

DR. KING: Dr. Morison?

DR. MORISON: Yes.

DR. KING: Dr. Epps?

DR. EPPS: I think that should be included. You could say something to the effect of it has been reported during trials or in experimental animals or something like that.

DR. KING: Dr. Tan?

DR. TAN: Yes, included.

DR. KING: Dr. Raimer?

DR. RAIMER: I think it should be included also.

DR. KING: Is that sufficient? No. 5; what, if any, information regarding the DLQI outcomes would be useful to provide in the product labeling? Dr. Swerlick?

DR. SWERLICK: I think you include the information on the PASI score, the global physician assessment and the DLQI.

DR. KING: The whole schmear.

DR. SWERLICK: Right.

DR. KING: Dr. Taylor

DR. TAYLOR: I don't see any reason to include any of those in the label.

DR. ABEL: What is the usual? What is the standard?

DR. SEIGEL: We usually include critical efficacy data to the extent we think it is useful in guiding therapy. There is a lot of public discussion and conversation and conflict about the extent to which quality-of-life data are included because, in some cases, they simply reflect the same thing that the clinical data do. The patient disease is better so they feel better.

In other cases, they provide additional information and are probably usefully informative if presented in an appropriate manner. So we don't have a single uniform consistent approach there.

DR. ABEL: Then I don't think it is necessary. I think you could provide references.

DR. KING: Ms. Knudson?

MS. KNUDSON: I am worried about putting in the quality-of-life measures. It seems to me that they could be easily misinterpreted by

patients if they saw them and by physicians also.

DR. KING: Dr. Katz?

DR. KATZ: I would not include that. The other thing is the statistical difference was not very great in that so that would be--

DR. KING: Confusing.

Dr. Morison?

DR. MORISON: I agree with that comment. I think the PASI score is quite enough. I don't think you need that.

DR. KING: So you don't want any information?

DR. MORISON: I think apart from people who are actually interested in psoriasis, they don't really understand that particular score in any case.

DR. KING: Okay. Dr. Epps?

DR. EPPS: No; I don't think it should be included unless it is some generalized sentence, one sentence.

DR. KING: Dr. Tan?

DR. TAN: Yes; I think it should be included. You especially want to spell out the primary outcomes is the PASI 75.

DR. KING: Dr. Raimer?

DR. RAIMER: I don't have any special feelings either way.

DR. KING: I think we have two who would like to include something and those who say it may be confusing and not add anything.

Do you want to go ahead with VI, adults with other form of psoriasis?

DR. WEISS: Please.

DR. KING: Dr. Swerlick? Should the sponsor evaluate the safety and efficacy of alefacept in people who have other forms of psoriasis since we are really dealing with the issue of chronic plaque psoriasis. So what should they do? What must they do?

I am just reminded that you are the consulting eunuch so be sure you just talk and we don't vote.

DR. SEIGEL: We are not really asking for votes here.

DR. KING: You notice I did not have any yesses or nos, hands up. You can talk and say what you want.

DR. SWERLICK: I would like to see that study done.

DR. KING: Dr. Taylor

DR. TAYLOR: I think it should be done.
DR. KING: Dr. Abel?
DR. ABEL: I think there should be studies particularly with erythrodermia palmar, plantar and pustular, not necessarily guttate, which has a better prognosis.
DR. KING: Ms. Knudson?
MS. KNUDSON: I am not a physician and I am not a scientist. So I really don't know the answer to that.
DR. KING: Dr. Katz?
DR. KATZ: Yes; I think they should be done.
DR. KING: Dr. Morison?
DR. MORISON: I guess I am a little more selective. I would be in favor of looking at pustular psoriasis and erythrodermia psoriasis to see whether there are any particular advantages there. But marching through all those is going to be done by people in any case.
DR. KING: Are you saying that the chronic plaqelike psoriasis often evolves in erythroderma and pustular psoriasis and so they should keep with that as a severe adverse event or are you just saying they should follow it anyway?

DR. MORISON: No; I am saying a separate study of erythrodermia and pustular psoriasis would be very helpful.

DR. KING: Dr. Epps?

DR. EPPS: Yes; other forms should be studied.

DR. KING: Dr. Tan?

DR. TAN: Yes; I think it should be evaluated.

DR. RAIMER: I particularly would like to see pustular psoriasis studied.

DR. KING: We are providing a nonbinding, non-vote, opinion.

VI (B), children. I think it comes down to we may not be able to deal with this in a real time frame we have here, but if you wish us to give a sentiment, we can do that on 1, 2 and 3. Is that what you would like for us to do?

DR. WEISS: Yes.

DR. KING: Sentiment only. Dr. Swerlick, should alefacept be studied in pediatric patients with psoriasis. If so, what is the timing of the studies, premarketing, postmarketing. If we have approved it, what should the registry do about the children with psoriasis and alefacept?

DR. SWERLICK: I think you need a controlled trial within the pediatric population. The endpoints would be similar to the endpoints associated with adult psoriasis. There is a particular issue with childhood immunizations and that whole issue that needs to be addressed that is somewhat distinct from the adult population.

DR. KING: So you actually did No. 1, 2 and 3 altogether. Dr. Taylor?

DR. TAYLOR: I am in a medical center that has a pediatric dermatologist, so I don't see patients with psoriasis who are pediatric age. It is hard for me to have much of a feel for this. So I am not going to comment.

DR. KING: Abstain; right

DR. TAYLOR: Yes.

DR. KING: Dr. Abel?

DR. ABEL: I believe we should wait for accumulation of postmarketing safety data in adults before we proceed to studies in children. Unlike, however, atopic dermatitis, we are not dealing with infants so much as I believe older school-age children.

DR. KING: Dr. Knudson, do you want to pass?

MS. KNUDSON: No.

DR. KING: Actually, I wanted your input as someone who deals with this all the time.

MS. KNUDSON: Right. I very much would like to know what the incidence is in children. The bimodal figures that were given indicated from 16 to something and I didn't get any figure less than age 16. I have not sense of how often this occurs.

DR. KING: Dr. Katz, you know about this.

DR. KATZ: I don't see that many children with psoriasis, but it must be done premarketing not postmarketing. So I should think it should be restricted studies.

DR. KING: So you want to focus specific study on children addressing all these issues 1, 2 and 3. Is that the sense?

DR. KATZ: I would wait until further postmarketing occurred and then only do it in children premarketing.

DR. KING: Dr. Morison?

DR. MORISON: I wouldn't be comfortable advocating doing a study like this in children at this point in time until I had more information of what is happening in adults. The reason I say that

is because most children, and I do see a lot of children with psoriasis, not a huge number but quite a significant number, most of them are in their teens. It is extremely rare that they do not respond to, say, narrow-band UVB. I can't remember the last time I had to put a person on a systemic agent.

So these people are reasonable cared for at this point in time. To turn around and ask the company to do a study with their present knowledge in a group of children is sort of like--well, I wouldn't be comfortable with it.

DR. KING: Dr. Epps?

DR. EPPS: I would wait until there was more data in adults. If you are going to select a pediatric population, I would be more interested in the ones with--whether or not it would be helpful with the psoriatic arthritis and psoriasis patient group because they are often on methotrexate. They are often on other medications.

If it would benefit other--their arthritis as well as their skin or if it had some kind of effect there, that would be wonderful because the arthritis is particularly disabling. So, as far as efficacy in the others, I agree. It should be

premarketing so, at this point, not approved for children.

DR. KING: Dr. Tan?

DR. TAN: Yes; I think the study for the pediatric patients should be delayed and wait for further data on adults.

DR. KING: Dr. Raimer?

DR. RAIMER: I agree. I would not feel comfortable treating children at this point in time. Possibly revisiting the issue a couple of years after the drug has been on the market might be a reasonable thing to do.

DR. KING: I think the issue is quite simple that they don't want to do it right now. If there is going to be a target population, it would probably be psoriatic arthritis, extremely rare. The sponsor may have difficulty getting those patients and they certainly respond differently to a lot of therapies.

Can we then skip to concomitant HIV infections? Given the effect on lymphocyte depletion, please discuss whether patients with concomitant HIV infections should be studied. Dr. Swerlick?

DR. SWERLICK: That is a tough one. It

seems to me that those patients would be at a particularly high risk of opportunistic infections. However, they probably represent a subpopulation of patients who have much higher risk, in fact, from using other immunosuppressive medications. So I don't think I would be particularly averse to the trial that is a separate trial to treat patients with HIV disease, but I certainly wouldn't recommend it on the label.

DR. KING: What would you put on the label? Contraindicated?

DR. SWERLICK: Yes.

DR. KING: Just trying to pin you down because I think that is what they want to know.

DR. SWERLICK: Yes.

DR. KING: Dr. Taylor

DR. TAYLOR: I agree this is kind of a tough issue. I would think that, once it is on the market, that those people who take care of people with HIV infections are going to study it one way or the other. You will have some knowledge about it in a fairly short period of time.

I don't know that you should label it as prohibited for those patients. Maybe something that is a warning.

DR. KING: Do you want it in a black box?

DR. SEIGEL: I just want to say, as a matter of practice here, that for theoretical concerns that haven't been studied, our tendency is not to write something like this as a contraindication. First of all, it makes it very hard to study it because of liability concerns. So often a warning simply that there are not data and there are real concerns works better in terms of alerting people, allowing people to do the studies or consider the options.

DR. KING: We understand. That is why we are trying to get it out there. If you just put it in in the warning box, then you alert the appropriate people as to what may happen.

Dr. Abel?

DR. ABEL: I think it has to be in there that HIV infection was an exclusion criterion in the clinical trial so that we have no data on that. That should be a warning.

MS. KNUDSON: I concur, absolutely.

DR. KING: Dr. Katz?

DR. KATZ: I agree with that.

DR. KING: Dr. Morison?

DR. MORISON: I sort of agree with it and,

also, I guess we haven't addressed the issue of what you are going to screen for before you put a patient on this drug. We haven't discussed that issue. I personally would be doing--I treat a lot of HIV-positive patients who have psoriasis. I would, myself, be doing an HIV test before I put them on this just as I do with the few people I put on cyclosporine.

DR. KING: So that is your recommendation, that, before you deplete the T-cells, you would like to know what their baseline is and whether they have HIV positivity?

DR. MORISON: Yes. But we haven't really discussed that issue.

DR. KING: No; we haven't. That is why I was trying to bring it up for the FDA--

DR. MORISON: I would screen them for hepatitis. I would screen them for HIV before I put them on a drug like that.

DR. EPPS: I agree with Dr. Abel, a sentence to the effect that it was an exclusion criterion and it was not tested in patients with HIV.

DR. KING: Dr. Tan and Dr. Raimer?

DR. TAN: Yes; I agree it should just

reflect the people--have the caution there.

DR. RAIMER: I agree.

DR. KING: At this point, I am supposed to, I think, ask the FDA who can ask whatever question they want remaining. I don't know about asking the sponsors because, as a substitute driver, I am not sure what racetrack we are on here.

DR. SEIGEL: That was, I think, a remarkable job of providing outstanding advice on a broad variety of issues. I think at this point, there is still, obviously, work ahead as advised by the committee but we are quite satisfied with what we have heard today and we thank you very much.

DR. KING: I have turned it back over to the Executive Secretary of her to declare where we are and what we are going to do next.

MS. TEMPLETON-SOMERS: I think we are done. Thank you very much for coming.

[Whereupon, at 4:15 p.m., the meeting was adjourned.]

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