there might be is some differences, then, in let's say immunization responses or some other acquisition of acquired immunity in some early childhood period when immunologic memory is being acquired.

So I wouldn't want to go back too early in terms of kids that are exposed.

DR. VAISHNAW: Thank you, Dr. Krueger.

DR. STEVENS: Thank you. To follow up on Dr. Morison's question, you have shown data that does not appear to affect primary immunization or transition from naive to memory in a T-dependent humoral immune system as well as minimal effect, possibly, in the recall cell-mediated immunity system. Do you have any data about the transition of naive to memory in cell-mediated immune process such as contact hypersensitivity or in DTH, itself?

DR. VAISHNAW: We don't have that. We have been working with the agency throughout the program to try and conduct immune test systems that are reliable, reproducible across multiple centers and where we can interpret the data. You have seen two aspects to that. You have seen the DTH and we have discussed the pros and cons of that data there. You have seen the other approach which has

been more robust across multiple centers, and that is the phi-X approach.

But we don't have data to that point. The only point I would make is given that some of these things are difficult to assess in a controlled fashion because of the types of assays involved, we have repeatedly asked ourselves the question what is happening in the safety database.

The corollary to a defect in the kind of conversion you are talking about is evidence of opportunistic infections or a pattern of infections that are suggestive of problems in terms of T-cell immunodeficiency and we have failed to detect that.

I guess my concern also didn't come only from infection but also the hint that, perhaps, there may be an increase of malignant risk in treated patients. So it was more that rather than infection that was bringing that concern

DR. DRAKE: Dr. Morison has a comment.

DR. MORISON: I would agree with that. That is the reason I raised the DNCB assay, an assay which is reproducible across multiple centers. It is an easy assay to do. There is correlation, at least in the mouse and, to some extent in the human, that if I had to develop a DTH

response to a contact sensitizer like that, it is correlated with the development of skin cancer.

So there is good reason for doing that, not just looking at the immune system and it is quite separate and distinct from the infector in infectious diseases.

DR. VAISHNAW: With respect to the point of the potential for a signal in the malignancy situation, maybe I could just review the squamous-cell carcinoma rates that we observed because squamous-cell carcinoma in many other settings where there is high intensity of duration or immunodeficiency is a good signal for occurrences of--it is a good sentinel event indicating significant immunodeficiency.

[Slide.]

In the placebo-controlled comparisons, I think both Dr. Marzella and my colleague pointed out that there was a numerical excess of squamous-cell carcinomas in the alefacept-related patients. Because of the excess numbers of patients in the alefacept group versus placebo, in those comparisons, we have been concerned whether it is a kind of false-positive signal.

The only way we have found to try and

contextualize the rates we have observed is this type of comparison where you look at the rate in the alefacept placebo-controlled studies at 12.5 squamous-cell carcinoma per 1,000 patients years, in the entire alefacept database, where we have 1,056 patient-year experience, you can see the rate is stable. It is 13.3. These are patients that are going over multiple courses.

So, if there was significant ongoing immunosuppression, one might detect an elevation in this rate here. Finally, at the bottom, you see the expected rates that Drs. Stern and Margolis and others who have been trying to address this issue in the literature have documented.

So, at least from these comparisons, at present we have concluded that the rates that we have documented are within those expected. In the sense of what is in store for the future, clearly, as we indicated and as Dr. Marzella indicated, this is a topic that is going to give continued study for us because we are obliged to do that. It is new therapy and a registry should help us address that.

DR. DRAKE: Dr. Stevens, are you done?

DR. STEVENS: I had another question on

the topic, if somebody had a follow-up question--

DR. DRAKE: You have another question. Dr. Abel, was your comment on this?

DR. ABEL: It relates, in a way, to side effects and skin potential carcinogenicity and skin cancer.

DR. DRAKE: Is it a question or a comment?

DR. ABEL: It is a question as to whether we have data, and you may have mentioned this already, in the patients who did develop cutaneous malignancies, what their prior treatments were that made them at risk; in other words, the PUVA-treated patients would be, perhaps, at greater risk.

DR. VAISHNAW: We can go through that.

DR. ABEL: Cyclosporine.

DR. VAISHNAW: I haven't shown you the data but we have those data for you if you wish to review them. Would you like to do that?

DR. ABEL: I don't know if we need to do that now.

DR. DRAKE: That is sort of borderline between question and discussion.

DR. ABEL: It brings up issues as far as recommendations and contraindications with regard to prior--

DR. DRAKE: It brings up all kinds of issues. If you would just address the facts and then we will do the discussion this afternoon. If you have a factual slide you want to show us.

DR. VAISHNAW: There is a factual slide.

DR. DRAKE: I figured you had one. You are very good. I am impressed.

DR. VAISHNAW: I will ask my colleague, Dr. Vigliani, to step up and walk you through this. It is a little bit busy.

[Slide.]

DR. VIGLIANI: These represent each of the individual patients who experienced squamous-cell carcinomas within the study population. We have indicated here the patients by course as to when they developed these squamous cells. What you see is that the majority actually were observed within the first course and then there were additional squamous cells reported in subsequent courses, although the subsequent course diagnoses of skin cancers actually were restricted to a couple of patients who seemed to be experiencing multiple--if we take the first patient, for example, in looking at the baseline history, we see that that patient who accounts for, actually, a total of six

squamous-cell cancers had a prior history of squamous-cell cancers, had a prior history of PUVA as well as UVB, methotrexate and cyclosporine.

So you see that there are a number of preexisting risk factors based on prior therapies as well as, in some patients, prior history of squamous cell.

We actually have a slide that looks at baseline characteristics that just defines this across the entire database.

[Slide.]

In this slide, what you see are some baseline characteristics of the patients indicated on the left. On the top of the slide, you see the proportion of alefacept-treated patients who developed squamous cells and/or basal cells and how these risk factors compared to patients in the entire alefacept population.

So, looking at a prior history of squamous-cell or basal-cell, what you see is that, for squamous cells, 25 percent versus 1 percent developed squamous cells had a prior history of squamous cell. You can see similar imbalances for prior treatment.

So I think what we can conclude from this

is that patients who developed these cancers were patients that were at high risk.

DR. VAISHNAW: I think the other point that, perhaps, we should make here is that, at baseline, we noted that, given that squamous-cell carcinoma, itself, is a predictor of subsequent risk of squamous-cell carcinoma, there was an imbalance between alefacept and placebo groups. The placebo group was one individual that had had a previous SCC. In the alefacept group, there were eleven individuals. So that, perhaps, also plays into the debate.

DR. DRAKE: We are running into lunch time and I want to make sure people have time to grab a bite to eat because people get cranky when they don't eat. We don't want to fool around with that.

I have Dr. Katz left on my list and Dr. Swerlick left on my list. You are okay? No more questions? Anybody else with questions?

DR. STEVENS: I still have one more question. I yielded for the follow up.

DR. DRAKE: You yielded for the follow up. I understand. So you are next and then Dr. Katz. Dr. Raimer, do you have any questions?

DR. RAIMER: No.

DR. DRAKE: Ms. Knudson, do you have any questions?

MS. KNUDSON: My questions have to do with adding children and that can come later.

DR. DRAKE: Okay. So we will do Dr. Stevens' last question and then Dr. Katz' question and then we will move to lunch and then reconvene.

Dr. Stevens?

DR. STEVENS: Thanks. I am trying to integrate all the information that you gave us with respect to the CD4 counts effects on--or T-cell counts and the effect as well as potential safety issues. You showed us that it took about six weeks to really knock out the T-cell population, yet you were dosing for twelve weeks.

I wonder about the variability between patients in their attainment of that lymphopenic state or relative lymphopenic state. I want to get an understanding of why the monitoring is at 250 cells per microliter, why that, maybe, is a magic number. Could we increase the potential safety or further ameliorate the safety questions by raising that threshold to a higher point.

There were a number of patients in whom you withheld doses because of the lymphopenia. So

the question is was this repeated lymphopenia in the same patients or one episode spread out evenly among a number of patients. I guess, ultimately, what I am getting at is trying to understand the cutoff for holding the dose and also the rationale behind the twelve weeks of dosing rather than some other number.

I guess the other factor that plays into that is the amount of time after you have finished dosing patients in which they maintain this relative lymphopenic state.

DR. VAISHNAW: So there were several questions there. Let's go one by one. I think the first one was the issue of the rates of dose omission because of a CD4 count under 250. If we looked in the Phase 3 studies, obviously the most controlled setting, 10 percent of patients in the IV study had that kind of transient dip and needed a substitution. It was 5 percent in the IM.

Then you mentioned the issue of, well, are there patients that get a more kind of multiple count below 250 and would require multiple substitutions. Indeed, there were 2 percent of patients in the IV study had that type of event in the first course and when the same patients were

retreated in the second course, there were none. For the Phase 3 IM study, no studies had multiple counts under 250 of the type you describe.

Now, the question of the choice of 250 has been important to us. We have thought very hard about it. The low limit of normal is 404 for CD4 T-cells. A CD4 count of 300 was elected in the Phase 3 studies. We saw very encouraging safety profile with that.

For Phase 3, the agency worked with us on the designs on those studies and they were aware of the threshold that we picked which was 250. You have seen the safety, efficacy and other data in relation to regulating dosing around that threshold.

A couple of things, looking back at this whole experience maybe that are important to acknowledge is that we have been intrinsicly conservative and we should have been and we are because we don't understand everything there is to understand about alefacept lymphocyte safety and efficacy although I might act as if I might.

We have a lot to understand and we want to be conservative. We have a count of 250 because we understand the safety profile around that now. We

propose moving forward with that. As multiple-course experience increases and our safety profile is defined over multiple courses, I think we can revisit the issue of whether 250 is or isn't. At the moment, we have data that supports 250 as a rationale choice.

The final thing I would say about the choice of 250 is that it is very much--it is all to do with what is happening in the blood. It does not necessarily mean that this is what is going on in the extravascular compartment. If you look at the individual patient profiles over time, and for those patients that got infections, you very often see a brisk rise in lymphocyte count far above normal, in fact.

What that teaches us is that we are looking in the blood. There is massive repository outside the blood and the function, there, of those lymphocytes is described by the safety profile and in the lymphoid tissues by the phi-X-174 experience.

So I have given a long-winded answer, but I think I have addressed most of your points.

DR. DRAKE: Dr. Katz.

DR. KATZ: Getting back to the clinical

study, and maybe I missed it in the briefing book, but the people who recorded these rather minor side effects like chills, were they the same people evaluating the patient for improvement?

DR. VAISHNAW: Whether people getting the chills were the ones that achieved significant improvement?

DR. KATZ: No.

DR. VAISHNAW: I'm sorry.

DR. KATZ: Was the same investigator the same physician evaluating chills, IM reaction, as was evaluating improvement in the PASI?

DR. VAISHNAW: Yes. So the clinical examination of patients was by a blinded investigator who was evaluating both the PASI and the physical status of the patient from the safety viewpoint; yes.

DR. KATZ: I may have missed in the briefing book, what percentage had IM reactions the first time?

DR. VAISHNAW: We can address that--I'm sorry?

DR. KATZ: What percentage of the patients getting the drug had that?

DR. VAISHNAW: I will ask my colleague,

Dr. Vigliani, to walk you through the data that we have addressing that.

DR. VIGLIANI: As I mentioned in my presentation, if you look at the overall integrated database, you would actually find that less than 5 percent of patients had injection-site reactions. However, we did see a higher frequency in the IM study.

I will just present to you here the data on injection-site reactions from that study.

[Slide.]

What you see was that there were 8 percent of patients with an injection-site reaction in placebo, 13 percent in the 10 milligram and 19 percent in the 15 milligram. These are any injection-site reaction.

If you look at the number of injections that were associated with an injection-site reaction, counting the total number of injections, you see that the majority of injection-site reactions were reported on one occasion, some on two and infrequently with multiple injections.

[Slide.]

Just to further characterize the injection-site reactions by severity, on this next

slide, what we see is that the majority of injection-site reactions or 84 percent in the 15 milligram group were mild, 16 percent moderate and no severe injection-site reactions.

In the IM Phase 3 studies, we had no patients discontinuing due to injection-site reactions.

DR. KATZ: I would like a comment, perhaps, from the group statisticians, as far as blind goes, I was concerned about the severity of the injection-site reactions. Do you think this, in part, negates the blind of the study because there is 11 percent more injection-site reactions seen by the physicians evaluating that, number one, and, number two, the 6 percent chills versus 1 percent.

Considering the margin of efficacy, we are talking about 10 percent, 25 percent. Are we talking about something relevant? Can we have the statistician comment on that?

DR. VIGLIANI: Can I just put back up the injection-site reaction slide again, that first one, just to look at what types of injection-site reactions these were, or maybe I don't need the slide. But the most frequent injection-site

reaction actually was just injection-site pain. No; I guess I don't have a slide of that. Sorry.

So the most frequent injection-site reaction was pain.

DR. KATZ: It was 19 percent versus 8 percent. The other thing was on the chills. I have another question for Dr. Lebwohl and then I am finished, Lynn.

DR. DRAKE: That's fine.

DR. KATZ: Mark, first of all, thank you--

DR. DRAKE: Mark, how come you keep standing between us and break? Have you noticed that this morning?

DR. KATZ: Mark, thank you for your clinical slides which had answered questions of mine, not being used to these studies, what is 50 percent, what is 75 percent. I certainly would agree with you that 50 percent is, in a clinical basis, very much appreciated by the patient.

I would revise my thought that 50 percent isn't so great and would agree with you that is quite impressive. However, you used the figure of 60 percent of people comparing to methotrexate. I am sure, clinically, that is going to be a clinical judgement for everybody and I appreciate your

experience because you have more than anybody else.

But you say 60 percent respond yet, even with a PASI of 50 over the placebo, there is only 24 percent response. That is in the IM study. There is a 9 percent clear or almost clear over placebo. So when you consider the experience we have with methotrexate of whatever--Figure 1 in the briefing book, it said 60, but I think usually 85 percent is quoted and they get equal response. I wondered why you would say you would pick this over methotrexate as a drug.

DR. LEBWOHL: First of all, largely because of toxicity. I think first the hepatotoxicity, which is long-term, which I think we can monitor for, but secondly those occasional instances of pancytopenia that happen because of accidents that happen out there. I view methotrexate, at least with what we know about it and, admittedly, we don't have long-term data on alefacept, but short-term, I do believe that this is a safer drug.

That is why I would put this ahead of methotrexate. As far as efficacy, no question methotrexate is a highly effective therapy. I think that before we started using PASI 75 or clear

or almost clear as endpoints, if you ask me how often does it work for methotrexate, I would say 80 percent of the time.

You said 85 percent of the time. I think if you applied the same bars, you would find the numbers probably a little bit higher than alefacept but not as much as you think. Someone told me that there was a poster at the SID that did that and, in fact, found the two comparable.

Lynn mentioned the October meeting of the FDA in which this high bar was discussed. Part of discussion was even if only 5 percent of patients achieved the endpoint because they knew they were advocating very high endpoints, as long as it was statistically significant, it would pass.

I think that what we are looking at here is precisely that scenario. You know, we are looking at the drug that the patients were very happy getting, the patients who responded were ecstatic getting. But a lot of the patients who were ecstatic didn't achieve PASI 75 exactly two weeks after they finished dosing.

The other issue that you mentioned with Dr. Vigliani I want to say that the chills were in the IV study, I believe. Is that right? In the IM

study, I don't think the chills occurred. I don't recall. I don't think that, to the investigators, that pain at the site of injection certainly didn't lead us to believe that that was active or placebo. That was only the first one or two injections.

So I don't think that we could have distinguished the patients on the basis of pain at the site of injection and the chills were in the IV study, not the IM.

DR. KATZ: Thank you.

DR. VAISHNAW: Could I just add a brief comment to that. The database that we have is interesting to probe from a variety of viewpoints and it gives interesting insights into the unmet need in this population.

About 10 to 20 percent of patients at baseline had abnormal liver-function tests. I think it kind of underscores the point that Dr. Lebwohl has just been making about the potential for the current agents and where the scope of new agents is to help patients like that. 10 percent of patients had a hypertension at baseline and they would be concerned about cyclosporine.

DR. DRAKE: What I would like to do now is two things. First of all, I want to thank the FDA

and sponsor for wonderful presentations. I have no doubt that the sponsor will hang around for this afternoon for the discussion. That is sort of a given.

But I would also hope that Dr. Lebwohl and Dr. Krueger, your comments and your expertise have been most appreciated and I hope you will be available to the committee this afternoon if we have specific questions. We would very much appreciate it.

Let's aim for--I this is a short lunch. I'm sorry. But still we need to try to aim for 1:30 because of the public comment. We are in recess until 1:30.

[Whereupon, at 1 o'clock p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

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

[1:40 p.m.]

DR. DRAKE: With respect to this afternoon, we have a very ambitious agenda to say the least. I must compliment the FDA. These questions are terrific but there are a lot of them. The only critique I can make is this should have been a day-and-a-half meeting, I swear, because this biologic is a new one for dermatology.

We are asking lots of questions and the committee is involved. It is fun to see this kind of intellectual dialogue with everybody just trying to do the right thing here. So I am tickled.

I had a question or two that I wanted to ask. This is going to be directed towards the sponsors. I know it is all time-and-done, for the sponsor to be done, but I saved my question. Dr. Marzella had a slide that was on animal toxicity. I was interested because it was kind of before all the data was in.

What I was quite interested in is could the FDA or the sponsor--and, by the way, I gave both the FDA and the sponsor notice ahead of time that I was going to ask this question so everybody could kind of have their act together here, but I

want to know what the recent status of the animal studies are. I want an update because I think one of the most serious things that this committee will have to consider is the safety issue.

That is clearly foremost on everybody's mind and I want to know if there is an update, any more recent information, on studies with respect to animals and primates. Who has the information on that because there is always last-minute information but it doesn't make it in our book.

DR. VAISHNAW: I will invite my colleague from Biogen to comment on that.

DR. GREEN (BIOGEN): Good afternoon.

DR. DRAKE: You are?

DR. GREEN (BIOGEN): My name is James Green and I am referred to as the chief toxicologist at Biogen at times like this.

DR. DRAKE: Welcome.

DR. GREEN (BIOGEN): I am currently Vice President of a group called Preclinical and Clinical Development Sciences and I am intimately involved in this study as well as well as worked with the FDA on a number of these issues over the past.

To update briefly, I think what I will do

is just give you a general sound bite of what the overall profile of the safety program looks like for alefacept in animals. You heard the incidence of lymphoma, single incidence. That was one incidence of B-cell lymphoma that was observed out of 228 animals, primates that had been treated with alefacept, one out of 228 animals that have been treated with various courses of alefacept from periods ranging from three months to one year.

With the exception of the lymphoma that Dr. Marzella described and Dr. Green reported, the profile in primates is one that is relatively uneventful, no opportunistic infections for animals treated at high doses for periods ranging from one month to 52 weeks, for doses that are pharmacologically active and superpharmacologically active.

The hallmark tissue change that would have been observed consistently in studies of one-month duration up to 52 weeks would be a subtle decrease in the T-cell-dependent regions of the spleen or the lymph nodes. This is a truly expected effect. It is one that we have seen consistently between studies and, in fact, it is one that is very, very subtle in nature.

One of the comments that I will make about the 52-week study which is in contrast to some of the shorter-term studies which went from one month to three months is that 52 weeks of treatment is high-dose intensity exposure, that is consecutive weekly dosing.

It is very different than the clinical regimen and the intent of that study is essentially to identify possible alerts or possible flags. We view, and I don't think we have any disagreement with the agency on their interpretation, is that the observation of this single lymphoma in heavily treated long-term immunosuppressed animals is not unexpected and, in fact, could be viewed relative to other immunosuppressive agents and put in that context.

DR. VAISHNAW: Just if I would close that comment with some clinical commentary. As Dr. Green just discussed, indeed cyclosporine-associated lymphoma is also well-recognized in the nonhuman primate starting at therapeutic regimens. The prevalence of those in the nonhuman primate setting is about 25 to 30 percent in the similar species when parallel types of studies have been conducted.

You have heard about the prevalence for us. The clinical implications are clear to us.

[Slide.]

I can probably just close that last point with this.

DR. DRAKE: I knew you would have a slide. I just knew it.

DR. VAISHNAW: In the cynomolgus monkey setting, if you look here on the far right, post-transplant lymphoproliferative disorder which are B-cell tumors occur at a prevalence of 25 to 30 percent in association with cyclosporine. So we have a similar situation here that, with alefacept, we have observed the one B-cell lymphoma. The prevalence is nowhere near this, of course, but it is a finding of note.

We are taking that data seriously. In the clinical setting, we have observed no B-cell lymphomas related to immunosuppression and we have clearly made this a subject of long-term study and we know we will have to study this in the post-approval setting as appropriate.

DR. DRAKE: Dr. Seigel?

DR. SEIGEL: Just to be clear, then, you said this is not unexpected in heavily treated

animals and you pointed that out. But you wouldn't have expected this to occur spontaneously without treatment, this sort of lymphoma; is that right?

DR. GREEN (BIOGEN): I think the experience in nonhuman primates is that this is a rare observation. These is relatively healthy animals and, in fact, the conditions that have been described long-term, high-dose, heavy pretreatment are associated essentially with this kind of observation that has been viewed in other contexts.

I think the important point with that cyclosporine is that cyclosporine dose is the therapeutic dose. In fact, that data was reported several years ago at an advisory committee meeting, a subcommittee of the xenotransplantation group that was held with CBER.

DR. DRAKE: I saw Dr. Green step up to the table from the FDA. I would like your comment on my same question, please.

DR. GREEN (FDA): The most recent report we have had from the company was last week, approximately. At that time, they reported to us the end-line portion of the 52-week weekly dosing study in cynomolgus monkeys. In the original form of this study, which was a nine-month study, there

was the incidence of the lymphoma that was observed and then that was converted to a twelve-month study which has just ended and now a one-year observation period has followed for the surviving monkeys.

But I think of the findings which was somewhat surprising, at least to me, was a treatment-related localized hyperplasia of B-cell lineage which occurred in three of six low-dose animals, 1 milligram per kilogram, and five of five of the high-dose animals which was the 20 milligram per kilogram.

The importance of this finding is that it is unclear as to what its origin is. It might reflect a reactive or adaptive response but it cannot be distinguished even by the committee we have had from reviewing pathologist from those cases which might represent an immune-suppressed related hyperproliferative response.

So you have basically the situation of T-cell suppression against a background of B-cell proliferation in which there is, in the animal who had the B-cell lymphoma, was also noted to have an Epstein-Barr-like virus infection which is common among these animals.

So the one-year observation period will be

an important aspect of determining the safety profile of this particular biologic.

DR. DRAKE: This is very important for those of you who might have wandered in late. I apologize. We should have box lunches for the committee members prepared and we will try to do that in the future.

But I asked the question, for those of you who walked in late, what was the most--I was concerned about one of Dr. Marzella's comments about toxicity in animals. I know so many of you have been skirting around that issue and so I asked what the most recent update was because there is always stuff that they have that doesn't make it into our briefing book.

You have just heard the company and the FDA's perspective on it. So, if I understand this right, there has just been one case of lymphoma but there is also this B-cell proliferation that you are seeing, or hyperplasia, rather, that you are seeing in this group.

We are not quite certain what that means. It could be a precursor or it could be. Dr. Green from the FDA, would you clarify that just a little bit more for me?

DR. GREEN (FDA): I think you are exactly right. It is not known. I think it was surprising that there was a hyperproliferative research. The consequences of that hyperproliferative response are basically unknown. They could possibly be the harbinger of something adverse or they could be a normal response which, over the course, the recovery period, will diminish and not present any issues.

But, at this point, that is an unresolved point.

DR. GREEN (BIOGEN): I think the other perspective that I could add to what Dr. Green has added, again, viewing the B-cell hyperplastic responses within the context of the single incidence of lymphoma. We have had these observations extensively peer-reviewed by veterinary pathologists and human medical pathologists. The conclusion that they reach is they say, well, this is not an unusual kind of hyperplastic finding that we see in heavily immunosuppressed patients, patients that would be in the transplant setting.

In fact, those animals that would have been in the transplant dataset that Dr. Vaishnaw

showed, if looked at histologically, it would not be unusual to see those similar kinds of changes. They are categorized and recognized as uniformly being reversible, nonneoplastic and it is not with any probability that they progressed to anything more serious when treatment is stopped.

We have other nonhuman primate data in the registration submission that hasn't been discussed here. But these studies have incorporated long-term recovery periods and, as part of our peer-review process, we have gone back and looked--these are very, very subtle changes. It is only with hindsight and foreknowledge of the single incidence of lymphoma that these tissues have been looked at very, very carefully.

What we have found is that we had seen focal evidence in previously conducted studies of the same kinds of findings, but when these animals essentially were put on long-term recovery periods, upwards of seven months, they completely reverse. So that pattern is consistent with what I think the human experience has been in patients that have been heavily immunosuppressed.

DR. DRAKE: Dr. Green?

DR. GREEN (FDA): Just to provide a little

bit more information, as best I recall, there were two longer repeat-dose studies in nonhuman primates. One was a seven-month baboon study and the other one was a 44-week cynomolgus monkey. The study that was recently reported to us in unique in the length of time that the animals were dosed.

As I recall, the 44-week cyno study didn't have similar findings. So it may be that some place between 44 weeks and 52 weeks, where just running this study again produced these results. I would also point out that, although there can be honest disagreements about how to evaluate this material, the lower dose, the 1 milligram per kilogram dose is, in our opinion, clinically relevant.

DR. DRAKE: But you said three out of five.

DR. GREEN (FDA): Yes; with the low dose

DR. DRAKE: At the low dose, and five out of five of the higher dose.

DR. GREEN (FDA): Yes. It is clearly a pharmacologically active dose.

DR. VAISHNAW: I would agree with Dr. Green that there are no findings that we have here that are not of clinical relevance in terms of

trying to understand their implications for us in the clinic. What we would say is that there is an opportunity here to identify a subset of events that we should focus on in the clinical setting. In dosing 1500 individuals at the clinical regimen, which contrasts very significantly with the regimen that has been explored here in this nonhuman primate setting, both in terms of dose, in terms of duration and in terms of the intensity of exposure, that we have not had any immunosuppression-related lymphomas or lymph adenopathy in the human setting.

But we cannot disagree and acknowledge that this is data of clinical relevance and something that has to be the subject of studies as the database expands in the postapproval setting. We propose a registry type approach to understand the incidence, if any, of immunosuppression-related events like that.

DR. DRAKE: Thank you very much. I am going to move to the public comment.

Open Public Hearing

I am very delighted to see public comment. Sometimes, we don't have it at these meetings and so it is delightful.

Gail Zimmerman from the National Psoriasis

Foundation. Welcome, Gail. We are delighted to have you here.

MS. ZIMMERMAN: Thank you for that introduction, Lynn, and I am glad to be here in behalf of the National Psoriasis Foundation. I am President and CEO. The Foundation was founded in 1968 by patients and physicians interested in helping people with psoriasis and psoriatic arthritis.

We spend our time providing information to the public on psoriasis and also serve as an advocate, we hope, effectively on behalf of patients.

Our funding comes principally from patients and their families. 70 percent of our budget is from the public. 20 percent comes from the pharmaceutical and biotech industry. 10 percent of our budget, of that money, goes to our operating budget and the other 10 percent goes to special projects, principally medical education for physicians.

I am here today on behalf of the foundation to communicate our support for the approval of, if I may say, Amevive. The other word I stumble over sometimes, alefacept. We support

that approval because we believe very strongly that there is a need for more treatments. There are too few treatments out there for people with moderate to severe psoriasis.

I wanted to communicate the reasons we believe that and also I have brought three members of the Foundation who have psoriasis to let them share briefly their story with you on coping with the disease.

In the twenty years I have been at the Foundation, I have discovered it is difficult for many people to quickly appreciate the impact of this disease. It is physical but it has a tremendous emotional component that is often hard to grasp if you are not intimately involved in treating it or in working with patients.

I wanted to tell you briefly about a survey we did this last couple of months. We did a national survey funded by Biogen and Immunex-Wyeth-Ayerst. We went to them. We saw an opportunity to obtain funding to do a national survey, a public survey, to measure the incidence of psoriasis and psoriatic arthritis and to establish some benchmarks about treatment. We were trying to find out is it only our members that are in need of more

treatments or is everyone feeling the same way; is it a representative population.

So we conducted this study and we finished it in January. We defined moderate to severe psoriasis as anything over 3 percent BSA. Based on that, we concluded or estimated there are 1.5 million moderate to severe psoriasis patients in the country.

In surveying them, in taking a small random sample of that group, 78 percent said they were not currently on any systemic therapy primarily due to side effects of lack of efficacy. That is a big number. Frankly, that reflects what our membership has told us in our small member surveys. There is a great reliance on topical steroids, still.

So we feel very strongly that we want to encourage new treatments. We feel that Amevive offers a potential safety profile that makes it a tool, a desirable tool, to add to the physician's treatment kit. We think there are many patients out there that would like this therapy because of that potential safety profile and its ease of administration.

So, with that, I want to just conclude to

say that I brought three members. These members, two of whom have used Amevive, we have asked them here because we wanted to hear--this is their story to tell you how they felt after this treatment. The third is a member who is not on treatment currently, or has just started treatment, and who has been on every treatment out there for psoriasis just to give you a brief overview of how it feels to make choices today about treatment and to live with the disease.

Thank you.

DR. DRAKE: Thank you, Gail.

I guess the first one is Ms. Diane Lewis. There is nothing like hearing from patients who actually have to deal with this disease to understand how important it is that we have good therapies for them. You are really a hero to come tell us about your experience, sharing your life with us and we thank you.

MS. LEWIS: Thank you very much. Good afternoon. First, I would like to say that myself and the next two speakers are lay people. This is our personal testimony and we are nervous and I ask you please turn off your cell phones because that ring could really throw us off. So, person-to-person,

please turn them off. Thank you.

My name is Diane Lewis. My age of onset was nine after a strep-throat infection. I have had this disease for twenty-four years. My family has been members of the National Psoriasis Foundation since 1986. I am currently in treatment at the Psoriasis Daycare Center at the University of California, San Francisco, under Dr. Ku. I am using a combination of bath PUVA and topical steroids.

My list of treatments include natural sunlight, LCD 20 percent, topical steroids, Dovonex, anthralin, gacrimin outpatient, which is a combination of UVB and topical tars, systemic steroids, Accutane, methotrexate three times. I have had a liver biopsy and climatotherapy at the Dead Sea three times.

That is just about everything that you can possibly name. I have not been on cyclosporine. For the last twelve years, I have had a total time of either totally clear of less than 15 percent for only four months. That is not very much. I am generally totally covered. The highest I have ever been is 95 percent.

The time factor of treatments is

extensive. It is hard to balance friendships, career and a life with having to go to a dermatologist or a day-treatment center all the time. I have lost jobs over the fact that I had to go into gracrimin. They would not hold my job for me.

It has been also difficult for my education as stress is a factor and finals is always difficult and I have actually had professors and universities say to me, "But it is just a little skin thing." When I can't move and I can't walk, it is not just a little skin thing.

In the last twenty-four years, I have dealt with the shame that comes with psoriasis, of wanting to cover yourself, of feeling like you have no control over your body. It is very difficult. The bonus of that is yesterday, when I was riding the local metro, nobody would sit next to me so I got to sit all by myself and I wasn't crowded. You always have to find the silver lining.

There is intense isolation with this disease. It is very difficult to communicate what it feels like to constantly be in pain, itching, not sleeping at night, waking up stuck to your sheets because you are bloody, having blood stains

on your clothing and constantly having to dust yourself.

There is also a fear of rejection. This has affected my intimate relationships. It is very difficult for somebody you are involved with for you to say, "I'm sorry, but I don't want to be touched right now and, not only that, I don't want to be touched for the next three months." It destroys intimacy.

It is also hard in friendships because you don't want to burden your family and friends with constant complaining but sometimes it is how we feel. Growing up with psoriasis, it has been difficult, as I become an individuated person, to create an identity that is separate from psoriasis. As such, in my early twenties, I went into a severe depression for five years. For three of those years, I was afraid to leave my home. I would leave my house once a week to do my grocery shopping and to see a therapist.

I was a total victim to this disease and I have slowly climbed out of it to the point where, in 1998, I was able to backpack by myself around the world.

There is also intense desperation

associated with this disease, desperation to find a treatment that works, desperation to find a doctor who can deal with it. Not many dermatologists can deal with the severity of my disease as they don't have the instruments. There are actually dermatologists who don't have phototherapy in their offices and they will put you right onto methotrexate or they will just keep giving you topical steroids because they are not comfortable giving you systemics.

It is very difficult finding a dermatologist who can deal with this and I am very lucky that I live in San Francisco and that I have the Psoriasis Daycare Center where they are able to give me a variety of options. Nonetheless, I have to accommodate this disease. I have had to find a profession that will allow me to have total flexibility where I can take off three months at a time to deal with my disease and be able to not work 9:00 to 5:00 as, in the mornings, I have to take two-and-a-half hours to go and have my bath treatments.

I live three blocks from the Psoriasis Daycare Center so that it is easy for me to go in the morning and get my treatments and not blow it

off.

It is also hard to find piece of mind. I want to tell you that, at one point, when I was depressed, the level of desperation and my desire to have relief would be that I would actually slice some of my plaques off with an exacto knife for that 10 seconds of relief so that the tightness wasn't there, so that the itching wasn't there, and it was the only way I could get it to go away knowing full well that, within 10 seconds, intense bleeding would start and I am sure immediate keratinization. That is desperation.

There are not a lot of treatments out there for severe psoriasis. I am a young woman. I want to keep my liver and I want to keep my kidneys. So I ask you to really consider this treatment. I am very honored to represent all the patients with severe psoriasis here in the United States.

Thank you very much.

[Applause.]

DR. DRAKE: Thank you very much, Ms. Lewis. Bless you for coming forward. It is very helpful.

Is it Ms. Maryellen Crawford is next?

MS. CRAWFORD: I am here today. I came with the National Psoriasis Foundation from Portland. I am Maryellen Crawford. I am a psoriasis sufferer. At the age of thirty-three, I was in a car accident and my elbows became very inflamed. The doctor said, oh, when you go home, they will clear up. They didn't and I was diagnosed with psoriasis.

Over the years, I have had as much as 75 percent. Now I am down to 1 percent, which is a joy. Living with the consequences of the lesions is difficult, both emotionally and practically. People staring at me, moving on buses and in movies, in plays, so that they don't have to possibly touch or come in contact.

Not swimming with my children in the local pool. I have never been told exactly that I can't go in, but you know they would rather I didn't. In the neighborhood, the children would ask my kids, "What is the matter with your mother? Has she been burned," or "Is she contagious?" and then maybe not coming to the house to play. Or, at school functions, they would ask me to volunteer. With the kids I knew once they would get a look at the legs or the arms that they would shy away, so I

didn't do it. I stayed home.

My husband also had to live through this. He lived through the bleeding, the itching at night. When I was near tears, he would comfort me. I wished, lots of times, that it would just go away.

Only wearing the long sleeves, summer and winter, not only for yourself the embarrassment, but the people around you would become very aware of how they felt and you didn't want them to feel uneasy. So, lots of times, you would stay home. You wouldn't go where you wanted to or with your children.

The bedsheets and the clothing would always be stained either with the blood or with tar treatments that you were on. The skin would become very, very tight and then crack and bleed and it made sleeping almost an impossibility. The scarring that you will live with the rest of your life.

Seeking medical help often was a nightmare. You would go from doctor to doctor getting tar treatments, different ones maybe, but the results were always the same. They didn't help.

I gave up going to the physicians because I was discouraged and just medicated myself with what I had learned through the years. Then, one day, I read a little article and it said that there was going to be a study and it had very little side effects. I jumped to the phone. I couldn't wait. That is when I read about Amevive. I was so excited that it had been tested in Europe with success and that it had supposedly very little side effect.

The drug Amevive, in the study that I was on, was an incredible experience for me. The side effects are minimal, just a little nausea after my shot and usually I go home and rest and I am just good as new. For the first time in all these years, I feel whole. There are days when I get up and I have forgotten that I have had psoriasis and the memories of the anguish and the embarrassment.

I would seek out Amevive in a second, even though it hasn't been approved. I was that thrilled. That is why I am so honored today to have been asked to talk about it. I just want to shout it from the rooftops. Everyone I know with psoriasis I have tried to tell them about it, that there is hope, don't give up.

Even though I am considered to have mild psoriasis, the hurt and the mental anguish has been no less difficult than someone with severe psoriasis. It is my hope that the committee would approve Amevive very quickly.

Thank you for the honor of being here today.

[Applause.]

DR. DRAKE: Thank you very much, Ms. Crawford. We really appreciate you coming.

Mr. Morton, welcome.

MR. MORTON: Thanks for having me. I am almost in tears. I have only had this disease for about three years so I am really an infant in the world of I guess wisdom, I should say. I really don't know where to start. I had something all written down so I guess I am just going to read it for you guys.

Imagine slightly bumping your elbow on a cupboard or a door and needing a band aid. Imagine combing your hair and ripping out the chunk of your scalp on accident. Imagine wanting to get a haircut but being too embarrassed to go to the barber. Let me ask you a question. Have you ever been in an accident where you have broken a limb or

maybe had a bandage and had people ask you, "What happened?" and, after while, maybe it gets a little bit annoying. If you have had psoriasis, you have experienced it and it is annoying.

I want to ask you also to picture yourself as a young man or woman, mid-twenties, maybe early twenties, and you have grown up so far normally, maybe played sports, had girlfriends, had boyfriends depending on your gender, I guess. Keep in mind, that you are in your prime, the time when you are supposed to be having fun and possibly finding your soul mate.

You wake up with this lesion on you. It is small at first and the next day, it is a little bit bigger. Then, over time, maybe it multiples. So you go to the doctor and he tells you try this and that and writes you a few prescriptions and you leave his office feeling absolutely no resolution.

A month or two goes by and you have been using the treatments, topical probably. They are not helping you. You go clothes shopping now no longer for what it is in style or what looks good on you but what will cover your hideous lesions.

Let's say once you were a happy person, maybe even good-looking. The good-looking person

you once were had degraded. You once played in the sun and now you just stay inside. Everything you once took for granted, like taking a shower or a walk or playing basketball with friends or maybe even asking out a pretty girl all seems awkward and uncomfortable.

Let's say you had good self-esteem which you thought was unbreakable. It wasn't. Unfortunately, that was me. I was on an experimental drug which had no noticeable side effects to me. It helped me be again the person I once was and, from my understanding, I have been on it for the last two years, it is not an absolute cure. However, it is a step in the right direction.

It is a little different from most or all treatments. Like I said, I haven't been as experienced as Ms. Lewis over there. But if you live the way I have for the last few years, believe me when I tell you that you would this drug also.

Thank you.

[Applause.]

DR. DRAKE: Thank you very much, Mr. Morton. We really appreciate your sharing with us.

Ms. Zimmerman?

MS. ZIMMERMAN: Excuse me, Dr. Drake. I just needed to clarify that our expenses for this trip out here, the patients and myself and the staff, were paid for by the Foundation.

DR. DRAKE: Thank you very much.

Dr. Menter? Welcome, Dr. Menter.

DR. MENTER: Dr. Drake, thank you. I appreciate the opportunity to come to speak to you today in this public forum portion. Basically, I would like to address three points. Number one, who am I. Number two, why am I here. And, number three, why do I believe new therapy is needed for the treatment of psoriasis.

From a personal point of view, why am I here? I have, just from a conflict of interest point of view--just as Gail said, I have paid my own way here. I am a consultant for Biogen. I have participated in clinical-research studies both for Amevive as well as for almost all the "biologic" drugs that are currently under development.

Basically, I have two brothers with psoriasis. I have lived with them for twenty-five years. They all live with us in Dallas. I have tended to their psoriasis and just like we have

very eloquently heard, I have gone through the struggles that they have had dealing with psoriasis.

I also had the fortunate experience of chairing the National Gene Bank for Psoriasis these last ten years under the auspices of the National Psoriasis Foundation and was able to travel around the country looking at families with psoriasis, large families with psoriasis, fortunately one of which was able to produce a gene for psoriasis for our gene bank.

I was amazed, just like you have heard today, how often fathers, grandfathers, kids, cousins, nephews when we got these families together, never knew that their loved ones has psoriasis. It is a hidden disease. You can just have to read John Updike's personal experiences in his book on how a psoriasis patient has to suffer.

Basically, it is a hidden disease and I think the time has come, just as we have heard today, for this psoriasis disease to come out and for people to recognize that this is as disease on a par with other chronic inflammatory disease, asthma, diabetes, arthritis, Crohn's disease, diseases of the autoimmune system, of the immune

system, that have a similar long-term chronic course.

So that is why I am here today. I also treat a number of psoriasis patients and have done for the last twenty-seven years in Dallas. We have a large psoriasis treatment center, just like you heard from Diane, similar to what Dr. Ku has in San Francisco. Currently, we have, at last count last week, 565 patients taking systemic therapy for psoriasis, the three main therapies you have all heard about earlier this morning.

So why am I here? What is the reason for me to come here and try to have ten minutes of time to speak to you about psoriasis. You have heard the quality-of-life issues from the patients. You have heard the presentations this morning about the drug, the efficacy, the safety data.

Basically, I believe there is a significant reason to have new drugs for psoriasis for one main reason. We have good drugs currently. The three systemic drugs currently, methotrexate, cyclosporine, Soriatane and PUVA, the light treatment, give us good results in I would say 60 to 70 percent of patients.

On the other hand, and I think this is

critical, we cannot look at psoriasis any more as short-term-treatment disease. Patients currently with all the treatments that we have, systemic treatments, relapse within six to eight weeks when getting off the drug.

We cannot keep patients long-term on some of these drugs because of the side effects you have heard about. So, from a quality-of-life point of view, it is critical that we look for drugs that will improve quality of life by improving remissions, either on treatment if it is safe or off treatment for longer periods than six to eight weeks.

A psoriatic hates one thing. They had being cleared and then allowed to relapse six to eight weeks later. They will tell you this. We need to look at psoriasis as a long-term, chronic inflammatory disease that needs long-term control like a diabetic takes an insulin shot every day, when an arthritis patient has to stay on long-term treatment. We need to find drugs that will allow us to maintain a stable course for these psoriatic patients out there.

From a perspective point of view, I have lived through Soriatane coming to the market. I

use Soriatane. I have lived through methotrexate. With methotrexate, we have a 30-year track record. I think Mark Lebwohl may have mentioned that three patients underwent liver transplantation for methotrexate. These are patients at our institution who have been overdosed with methotrexate.

We have a huge big transplant population at our institution in Dallas. Three out of the first 200 patients transplanted were psoriasis patients who had had too much methotrexate. So we cannot treat with cyclosporine for longer than a year, with PUVA for periods of time without skin-cancer risk.

So why, to answer my third question, do I believe we need a new treatment for psoriasis? I have polled, out of the 500 patients we have plus, between the three of us, and we do psoriasis treatments on a daily basis and psoriasis clinics on a daily basis, I have polled our patients, would you prefer a weekly injection, a monthly injection, recognizing there are other drugs coming down the pipeline that may have different manners of administration. This has been done. The British have published a publication showing, as well, that

the vast majority of patients would prefer a weekly or a monthly injection if this will keep them clear for longer periods of time than is currently available except for PUVA which does keep people clear for longer periods of time.

The vast majority of patients will tell you, give me a weekly injection. If it is safe, and I recognize this is a major problem with a drug that is new--not a major problem, but something that we all have to consider--but having started with cyclosporine in the 1980s where we didn't know much about it, methotrexate in the '70's that we didn't know much about, recognizing that those drugs took a long time to be approved, they have helped our patients but we need more.

We need more medicines available for our patients currently today. Half the patients drop out of treatment because of concerns about side effects and almost a third of our dermatologists in the country will not utilize systemic treatments currently.

Therefore, in the last two minutes, why do I believe we need a new treatment for psoriasis? I have talked about the current drugs we have available. They will continue to be utilized.

Dermatologists do a wonderful job in mixing and matching medications probably as well as any other specialty. I believe should this panel decide to approve alefacept that dermatologists will find the most expedient way to utilize this drug with safety criteria that dermatologists being fairly conservative people in the majority will recognize and understand.

Drug holidays off treatment is important to minimize side effects. I think I have already mentioned that the three drugs we currently have available we cannot get patients off these drugs for longer than six to eight weeks without them failing and sometimes failing fairly substantially.

So that is drugs with the safety profile that we understand, affording long-term remissions, are very critical. Too many patients have withdrawn from treatment, as I have said. I do believe that the problems that you have heard about so eloquently from the patients and the NPF are real and afford us the opportunity to take 6 million lives in the United States, improve the quality of their lives and improve the treatment that we currently have available.

I would urge the panel to take into

consideration all that has been said and consider not only safety profiles, not only improvement, but the tremendous need in the marketplace for patients to have better treatment.

The final point I would like to make is that psoriasis, as you have heard today, is a disease of young people. The vast majority of patients with psoriasis present before the age of 35 when body image is important. They are developing their body image. Those of us who are older recognize that our paunches are getting a little bit bigger and our hair is getting thin, but the bottom line is when a person is fifteen, twenty, twenty-five and their body image has not yet been established, looking at themselves in the mirror every day and recognizing their psoriasis is an important factor in their own self esteem.

Females have equal representation with psoriasis. Currently, a twenty-five to thirty-year-old female or a thirty-five-year-old female contemplating pregnancy cannot take any of the drugs we currently have available. So we need to have drugs available that have a safety profile that we can understand, we can follow, we can watch, we can be conservative and we can improve

the quality of life for our patient population.

Thank you, Dr. Drake.

DR. DRAKE: Dr. Menter, thank you for a very passionate and well-thought-out presentation. We appreciate your taking time to come.

I also have to tell you that I want to also thank Ms. Lewis for helping me make my announcement about the cell phones because I forgot again. So you helped me. So thank you very much. There is more than one way to skin a fish, isn't there. Thank you so much.

We do appreciate so much, Gail, you and all your representatives coming. It takes time out of people's days and lives but it is important for people to put these things in perspective. The committee has to weigh efficacy and safety, which I think is our foremost issue, it is important to hear from patients so we know why we are all here.

So thank you again.

Committee Discussion and Vote

DR. DRAKE: Now, here we go, group. We are down to the real serious nitty gritty now. We are now into just the committee deliberations.

The sponsor will be asked not to comment unless called upon during this time period because--it is as

much a time issue as anything, but this really is the committee's time to think about things and discuss it.

As you can see, we have a lot of questions. I have tried to have some time lines that are rational about most of this. I would like the committee to think about how much we have to cover and keep your comments as abbreviated as possible and pertinent. Maybe we can get through this agenda.

I may change the order. I am going to change the order just a little bit. I am going to take the Chairman's prerogative. We are going to take Roman numeral I first followed by IV because I do not want us to miss the crux of the issue with people, perhaps, having to leave or running out of time. Frankly, each one of these questions could take a day in and of themselves. They are wonderful questions and they are wonderful thoughtful propositions. So there was some real thought that went into it.

Roman numeral I, I am not going to read the whole thing but I would just like to highlight. Let's start with Part A. It is about lymphocyte reduction and risk of infection. Just to make a

few quick summary points, in Study 711, approximately half the participants experienced at least a single occurrence of the CD4 cell count below the lower limit of normal at any time during a treatment.

That was kind of a point. Then the next point the has been made is that the total experience of patients receiving more than two cycles is limited. The third point--these are safety concerns. You understand this doesn't rule anything in or out. With every drug we have these issues and so it is just kind of important to highlight them and see if we think the risk-benefit ratio is where it ought to be.

Third is a central issue, interestingly enough. It is where the lymphocyte reductions result in clinical sequelae. Serious infections were reported in about 0.2 percent of placebo and 0.9 percent of active drug in the treated patients. There didn't seem to be an apparent relationship between lymphopenia and infections and there were no opportunistic infections observed, which I think is important.

Then I think, in the fourth paragraph, one of the points I want to make is that normal

lymphocyte and CD4 cell counts were required before the first treatment cycle and normal CD4 cell counts were required for subsequent cycles. These are kind of the major points upon which the agency based their questions to us.

Have I given that an accurate summary? Dr. Weiss, do you have anything to add to that?

DR. WEISS: No; that is fine. Thank you.

DR. DRAKE: Okay, good. Depending how much the committee wants to get into, I think the first thing--the only one of all these questions, of all these Roman numerals, that we need to vote on today, so you will know that, too, is No. IV. Roman number IV is where we will have a vote. Otherwise, these are questions, discussions and I may ask for a sense of the committee, just a sense of what you are thinking, to give the agency some direction of how the committee is thinking, but they are not votes.

So has the sponsor generated sufficient data premarketing to characterize treatment-related effects on lymphocyte reductions? What say you? Listen to me. I have been listening to O'Reilly too much using his same quote.

Dr. Raimer?

DR. RAIMER: I think we do need to follow patients if the drug gets approved to watch whether we have a registry or exactly how it is done, I think the numbers of infections need to be monitored.

But I am very encouraged by the fact that we don't see opportunistic infections. These were over a fairly large number of months so I think if it were really going to be a very significant problem that probably would have shown up in the studies that have been done so I feel reasonably comfortable and not totally comfortable. I think it is definitely going to need to be monitored because it definitely is a potential problem. But I feel reasonable comfortable at this point in time.

DR. DRAKE: Dr. Swerlick?

DR. SWERLICK: I have a question regarding what level of safety we are talking about. We are able to identify, or potentially identify, significant infections in a patient population, about 1,300 patients extending over a few years. If we are looking for adverse events that are going to occur 1 in 10,000 or 1 in 100,000 or more, how many patients are we going to have to follow for

how long? Perhaps the people from the FDA can address that issue.

DR. SEIGEL: Following patients for rare events that have a significant background you could follow forever and not determine if you don't have a controlled population. If you are talking about rare events that are very uncommon in the population, certain specific types of tumors, liver failure or whatever, those will stand out in a postmarketing.

If you are talking about an increase in the incidence such as these data might suggest of something like cellulitis. That is certainly going to happen to patients without the treatment, I think the answer is, especially given that these patients will be on and off this therapy and several other therapies, that you will not know, outside of controlled studies.

DR. DRAKE: Bob, you just hit on the crux of the question, how do we know when safety is enough safety. I don't think this committee ever knows. Sometimes, you just have to keep tracking and see what happens. But I think the important thing is we don't turn something loose that we think might cause imminent harm would be the way I

would approach it.

DR. SWERLICK: I would like to know the standards so we don't set the standard in such a way that it could never be approved.

DR. DRAKE: I see.

DR. SWERLICK: If we set a standard that is so difficult--and I am trying to get a feel for where the standard is.

DR. SEIGEL: The laws and regulations speak to safe and effective and for biologics say pure and potent. I can tell you that the long tradition with the FDA and its advisory committees is that safety is certainly considered in the context of benefits. Many of the drugs that are used to treat cancer wouldn't be considered safe if used to treat a common cold or a simple headache.

So it is a judgmental risk-benefit but there is not a lot of formal guidance I can give as to what a standard is in that regard.

DR. DRAKE: Dr. Katz?

DR. KATZ: To go along with what Bob just said, isn't it difficult for us to discuss this in an isolated manner without integrating it with efficacy. I know, Lynn, that we have to discuss one thing at a time, but you are probably willing

to have certain risk if you are clearing up 90 percent of people. If you are clearing up 15 percent of people, maybe you are willing to accept lesser risk even in a disorder such as this.

As Bob said, we need a little more guidance before we make an agreement whether this is acceptable or not, an acceptable risk for this condition.

DR. SEIGEL: Excuse me, and let me clear up and in answer to Dr. Swerlick's question because I wasn't sure if you were asking what is the standard for how safe is safe enough, or how much data is data enough.

DR. SWERLICK: Both.

DR. SEIGEL: Because I answered the first one, but there is a guidance for how much data and it was alluded to in the sponsor's presentation. It is one developed in the international harmonization process which speaks about drugs for chronic disease and suggests that there should be--the numbers that come to my mind are in the 1,000 to 1,5000 range of exposures, 300 to 600 at least for six months of therapy, 100 for a year of therapy.

But that guidance is also full of provisos

where certain signals arise. Where there are concerns about serious rare events, you may need more or whatever. So it is to be taken in the context of the science. But that is the guidance given to provide an approach to identifying rare events that may occur in chronic therapy that are not anticipated.

There has been some discussion since those went into effect some probably seven or eight years ago, and given some the concerns about adverse events being discovered with drugs after their approval as to whether those guidances are adequate. For many drugs, we have larger numbers than that.

DR. SWERLICK: Basically, the first question points to use of surrogate markers to try to predict whether or not something untoward will happen in the low-frequency event. The difficulty with that is that we really don't know--even if we see drops in lymphocyte counts, how do we interpret all that?

I guess the crux of my question is that it is not really if something untoward will ultimately happen in one patient who is receiving this drug. If you give it to enough people, something bad is

going to happen whether it is related or unrelated. Ultimately, what is the frequency that we will find acceptable? Will that be 1 in 10,000, 1 in 100, 1 in 1,000? That is where I am uncomfortable because, ultimately, that is where we are called upon. And I don't know what the standard is.

DR. SEIGEL: Right. That is why I was answering the first part. That is determined in the context of anticipated benefits. There isn't a standard. What is acceptable in one disease and for a highly effective drug versus a less effective drug or for a more serious versus a less serious disease is going to vary and it is usually a matter of common--by saying it is common sense, I don't mean to say it is easy. It is not easy, but it is not a hard number.

DR. DRAKE: Dr. Morison.

DR. MORISON: I think one of the issues is how are you going to follow the patients, not just how many patients have you got but how are you going to follow them. The example immediately comes to mind is the multicenter study on PUVA therapy here in the United States. They followed 1,500 patients and, after about ten years, had about a 98 percent follow-up rate on those 1,500

patients and found an increased risk of squamous-cell carcinoma within two and a half years of the approval of the treatment whereas, by comparison, the European study has 3,500 patients that, after about five years, was only following 1,500 of those patients and it took ten years to find an increased risk of squamous-cell carcinoma.

So, when you are talking about a registry or following patients, I think it has to be clearly defined what you mean by following patients. Are you taking a population of patients and making sure someone is keeping tabs on those patients and looking at them at regular intervals because, otherwise, you could have a lot of ex-PUVA patients or UVB patients or sun patients out there with squamous-cell carcinoma and you won't detect them unless someone is very carefully following those patients.

So the use of the word "registry," I think should be defined rather than just drug registry.

DR. DRAKE: Let's discuss both parts of the questions then, of the first question and the second question, since we have kind of wandered into that.

Dr. Epps?

DR. EPPS: I guess I would like see more data although two cycles is more than one, I don't necessarily think it is multiple. Certainly, if, according to the testimony of people who have experienced this medication, if they really like it and they think it helps them, then certainly more cycles could be performed for longer studies and more data.

I think it would also be important to interview the people who dropped out, find out why they dropped out, who didn't have side effects, necessarily. Is it because they couldn't wait? Is it because they had an untoward effect or whatever. But I think that is important to know, too, collecting the pro and the con for any medication because, although we hear the testimony of people who benefit from it and, of course, we all want medications for psoriasis and more options.

I am in a pediatric group and my options are much more limited. I hear the stories of people won't hold their hand and won't play with them. So I am very aware of the other side effects, but I am also very aware of the long-term safety effects and we will get to the pediatric questions later, but I think if there are adults

who are willing to move forward and have multiple cycles, I think it would be important to collect that data.

DR. DRAKE: I think we can mix some of the kiddie stuff in with this right now. Everybody commented to me about kiddie stuff during break, so make your comments, if you will, just kind of right along with that. If we look at children right now, what do you think about this? Should pediatric patients be included in this now? That is one of the agency's questions.

Do we need specific studies in pediatric patients? You are a pediatrician.

DR. WEISS: Just let me clarify, too, that I think what is on the table, a question that we will hopefully get to, is Roman numeral IV, an indication for use in adults. The question, then, would be for pediatrics because the sponsor is not actually asking right now.

DR. DRAKE: I know that.

DR. WEISS: The question would be if and when to study children.

DR. DRAKE: I have a suggestion, then. In the interest of time and streamlining the process, this is an important clarification. The sponsor is

not asking for children. The children is sort of a second phase in the process. Let's focus our discussion now on adults and get through the primary adult stuff because this is not a request by the sponsor to do children.

So we could put that off and address that later, time permitting. Is that fair enough, Dr. Weiss?

DR. WEISS: That is correct.

DR. DRAKE: Good. We solved that. Boy, you saved me some time there. Good job, Dr. Weiss.

I want to ask a question. I want a sense of the committee. That second part, given that the sponsor is proposing the product be indicated for multiple cycles, please comment on the adequacy of the data to support multiple-cycle use. We have had data on two cycles.

I want a sense of the committee. This is not a vote. This is just a sense. Do you think that this data is sufficient at this time for us to go ahead and think about--do we need more data--I'm with you a little bit. The efficacy almost comes before the safety but do you think--let's for the moment assume that the efficacy was okay and we are thinking about recommending approval of this.

Do you think that we have enough data in terms of cycles or should, perhaps, the number of cycles given be limited initially until further data is collected? What is your sense of the committee? Dr. Abel, do you have a comment on that?

DR. ABEL: My sense is that there should be some limitation. If, indeed, the responses last up to nine months, then, hopefully, the responders are going to be the ones that will be treated. But the ones who don't show response won't have multiple cycles to try to push them to be responders and maybe increase the possibility of toxicity side effects.

There are some who aren't responders. I have to maybe get a better feel for the percentage but there are excellent responders, there are moderate responders and there are some that clearly may be nonresponders. But I would not like to see those nonresponders being pushed with multiple cycles to try to get them to be responders and just treat them every twelve weeks, I mean after only a twelve-week interim.

DR. DRAKE: Dr. Seigel and then Dr. Tan. Dr. Tan, did you have a comment on the--

DR. TAN: Right on this.

DR. DRAKE: Okay; excuse me, Dr. Seigel, he kind of had his hand up first.

DR. SEIGEL: That's fine.

DR. TAN: I think we discussed in the morning that we don't have--there really isn't enough data to differentiate the benefit of the second course is due to the carryover effect of the first course. So there wasn't enough data as we discussed in the morning, I think.

DR. DRAKE: Dr. Seigel?

DR. SEIGEL: I just wanted to make sure that the committee understood, as they discussed this and particularly since you asked the sponsor and they have been very compliant--they are remaining quiet--to note that there is two-cycle data in the controlled clinical trial. There is a limited number of experience with patients on third, fourth and fifth, I think 150-some odd on third and another 120 who have had four or five cycles.

They are subselect groups. They are not studied on the same controlled protocol but there is some experience available with additional cycles. Then probably in comparing, like,

lymphopenia issues, if you look at the 80 people who had four cycles or the forty-some odd who had five cycles, they are a subgroup, people who might have had certain types of either durable responses or unfavorable responses in early cycles aren't getting later cycles. It is a little hard to understand, but there is, indeed, some data available on longer cycles.

We are not comfortable, I think, with the amount.

DR. DRAKE: You are not comfortable with the amount? Okay. So the agency has got a level of discomfort. Solves that.

Any comments on how to discuss the optimal ways to generate additional data on infectious risks? Lloyd. It is 2 under A under Roman numeral I, please discuss optimal ways to generate additional data on infectious risks.

DR. KING: I had suggested one of the surrogate markers would be the C-reactive protein. There is a whole body of information, such diverse things as atherosclerosis, et cetera. The best predictor is not the lipid profile but the C-reactive protein as studied in the Framingham study of nurses.

So it seems to me that, if you are going to have cells, the question is whether they are potent or not; that is, the product being released could be an acute-phase reactant. So it seems to me that one of the populations that keeps coming up, diabetes, atherosclerosis, psoriasis and so forth, I, for one, believe that psoriatics are much higher risk as a subpopulation for atherosclerosis and heart disease than one would imagine.

Part of that may be the C-reactive proteins. So I would suggest that it is oftentimes difficult to culture things. We all have a lot of things--you can't culture strep from cellulitis. It is like 10 percent. So I would suggest measuring C-reactive protein and other parameters would tell you whether or not the up or down pool of T-cells did or did not produce the biological assassins.

DR. DRAKE: Bob and then Dick.

DR. SWERLICK: I would just inject a word of caution again using surrogate markers. The difficulty is that, unless you study that within a population of psoriatics who have not been treated with this drug, you don't know how to interpret it because the gold standard becomes whether you can

actually diagnose an infection or not.

Therefore, in order to generate sufficient data to know whether or not the drug sets people up for increased numbers of infections, you just have to follow a lot of people for a long period of time and compare them to controls that were followed for a long period of time. Otherwise, I am not sure how to interpret the surrogate data.

DR. KING: They already have data on psoriatic arthritis. So one of the ways, potentially, to get into the issue of children and psoriasis is look at C-reactive protein. They are already doing biopsies. I am not sure they are biopsying joints of children. So maybe our rheumatology colleague could help us more this kind of phenomenon, but I agree, you can't always diagnose infection. But if you have psoriatic arthritis and you are already getting response and you are measuring C-reactive protein as your surrogate marker, I am talking about that specific population.

DR. DRAKE: Dick?

DR. TAYLOR: I may have some confusion with regard to the registry. I am not sure what that is going to include. But it appears to me

that if the registry was inclusive enough, it could tell you about lymphocyte counts after four, five or ten cycles and it could tell you about the malignancies and it could tell you about some of these things that we are concerned about and maybe make it easier for us to worry about the efficacy and not so much about the toxicity.

So maybe somebody could explain what is going to be in the registry or maybe it could be expanded to include some of these things. Who is going to control the registry? Who is going to do it? Is it on all patients?

DR. DRAKE: With all due respect, I would like to ask Dr. Seigel have you guys thought about a registry? Where is the FDA on this?

DR. SEIGEL: I think the company has proposed one. Whether or not we would be discussing with them whether a registry is the right way to proceed will depend, in significant part, on the determination as to whether to approve the drug now. I think some of the issues can be addressed well in a registry. Other issues are better addressed with randomization and controls.

So, obviously, we are looking for some guidance and to make some guidance and to make some

decisions as to where to move forward. So I don't know that we have had substantial input yet as to registry design. We have not.

DR. WEISS: Oftentimes, registry discussion comes when we are talking about approving a product and then these would oftentimes required postmarketing commitments and we would discuss in much more detail at the time of an approval about the size of the registry and the amounts of data to be collected and the types of periodic follow up to the agency that would be coming in.

There are lots of details. There is a lot that can be done right now. There hasn't been much discussion in that regard.

DR. DRAKE: So we are not quite there yet. Since you stood up, and I don't, by any means mean to be rude, would country give us a quick sentence from the sponsor? But I really want to keep this committee-focused right now.

DR. VAISHNAW: The first half of the sentence is that there are over 800 patients in safety-extension studies and the current snapshot of the database reveals several hundreds in the fourth and fifth course is different from the

different you are reviewing right now. The safety profile remains the same. If that is helpful to that panel to know that.

Secondly, the registry study, we are in active dialogue with experts and we feel there are a number of good ways to move forward and definitively answer the question is the risk of something like squamous-cell carcinoma elevated and, as a sentinel event, our hypothesis would be that a discrete elevation in the rate of that would be telling in terms of potential for other types of risks, and this is a tractable problem.

DR. DRAKE: Thank you very much.

Seth?

DR. STEVENS: I would just like to comment, with all due respect to Dr. King, about the use of surrogates. I would agree that the way to follow infection is clinically to look for infection. I think that we associate things based on our clinical experience in the past. I think an example of that this morning was, for example, chills which we normally associate with infection.

There were chills. There wasn't strong evidence for infection. I think when using biological-response modifiers and things like that,

some of our old associations don't carry over. I think when the thing that you really are interested in is something that we are trained to do, that doesn't involve expense or risky tests, I think that is the best way to monitor for those events.

DR. DRAKE: Other comments on this first question, on this first section, on the safety, the lymphocyte reduction. Lloyd?

DR. KING: I am still concerned about this line that says who is going to follow up and monitor the lymphocytes if you turn it loose? It has been my experience there is a whole lot of off-label use and, once you open the door, it is the Harvard law that, under defined conditions, the organism will do as it dadgum well pleases.

The idea of the registry actually is intriguing to me because, having been involved in the fuss about Accutane back and forth, it seems to me that the study will get the results you plan for but it is the unexpected things that, if you turn it loose, people are going to be so--as you heard, "I want something, even if it is going to be dangerous for me."

Then, after the fact, after you have taken three courses of, say, arsenic for asthma you find

out fifteen years later it causes cancer. So I think the idea of registry really has to be hammered out and actually who is going to follow these people because if you just turn it loose and say all you have got to do is take a skin injection once a week, I can imagine that there will be whole lots of nondermatologists and other people doing this because it happened to me with Accutane. So I am concerned about the registry.

DR. DRAKE: Dr. Weiss and Dr. Seigel, what I am hearing, to kind of summarize what I have heard, is that the sense of the panel is that there probably needs to be a registry or some semblance of a registry, perhaps some follow-up studies, either before or after, preapproval or postapproval, but clearly some follow-up studies.

Probably two cycles is very limited information upon which to base long-term conclusions. So, as you get into multiple cycles, I think you are clearly going to need more information about what happens to lymphocytes, what happens to infections, what happens to the whole malignancy notion.

I think there are all kinds of things that would need to be followed out either before or

after approval. Is that a fair assessment from the committee's perspective? Lloyd?

DR. KING: Yes.

DR. DRAKE: Does anybody have additions or corrections to what I have just said? Dr. Weiss and Dr. Seigel, is that adequate for you guys? Do you need more information before I move on to the next one?

DR. WEISS: I think that is adequate. Thank you.

DR. DRAKE: Okay. You notice I didn't say is that exceptional because I don't think we have given you any exceptional help there. But I think we are a little baffled ourselves exactly how to proceed. So at least we can try to help you.

Let's talk about B, the changes in antigen response. In Study 708, the number of DTH shifts from plus to minus was higher in the treatment group compared to placebo. So let's look at the questions. Should all individuals be evaluated for latent t.b. infection with a tuberculin skin test prior to therapy? If latent infection is uncovered, discuss how such individuals should be managed with respect to use of this drug.

Comments on that question? Bob?

DR. SWERLICK: I don't think it should be any different than using any other immunosuppressive. Essentially, if you put somebody on prednisone or you put somebody on cyclosporine or Immuran, you are going to end up managing it the same way. So at least they have to be held to the same standard.

DR. DRAKE: I think that is a very simple answer to this question, just make it the same standard as other immunosuppressives. Any additions or comments to that?

DR. SWERLICK: The only other question about the PPD, it may be meaningless because these patients may have been put on other immunosuppressives which may modify it. So I think it has to be sort of determined, an algorithm depending on whether or not they have been on immunosuppressives before.

DR. DRAKE: Other comments on that question? Should subject monitoring include periodic assessment of DTH?

DR. SWERLICK: My comment on that it is such a miserable test. I am not sure to interpret it so it would be hard for me to require them to do that.

DR. DRAKE: I saw almost everybody at the table shaking their head no. So you got an answer there. Number 3, should the sponsor perform studies to evaluate the ability to respond to immunization such as pneumococcal or influenza vaccines? Lloyd?

DR. KING: If you are going to address the pediatric population or older people where you do that for--where they COPD, et cetera, I think the answer would be yes. I think you really have to talk about if you are going to vaccinate against Asian flu which may knock people out.

The same reason you knocked out the age population not getting this drug early on, I think you have to say that a recommendation would be high-risk populations, children and older people with disabilities, the answer would be yes.

DR. DRAKE: Help me, Lloyd. Are you saying we should not give it to these patients or do it with due consideration?

DR. KING: No, no. I'm sorry. I'm saying if you are going to give it to these populations, addressing the issue of children, then you are going to talk about is the immunization going to be effective.

DR. DRAKE: Let's talk about adults because we are not on kids yet.

DR. KING: Adults in high-risk populations, I think it should be periodically tested to see if they are going to respond to the flu shots or whatever in the same way you want to know if they are going to resist Asian flu or whatever. I think you are going to have to have populations you recommend testing.

DR. DRAKE: Other comments? Elizabeth?

DR. ABEL: I think this might apply to all of the potential side effects, change in antigen response, malignancies. We have talked about who are candidates for this treatment but I think we also have to think what population groups may not be candidates or what population groups there might have to be special cautions written up in the package inserts. These might be not just children but--well, we are not talking about children but previous treatment in regards to, say, PUVA or cyclosporine, geriatric patients, et cetera.

DR. DRAKE: I think what I am hearing, the sense of the committee is saying one needs to use reasonable and rational precautions in high-risk populations.

DR. KING: Yes.

DR. DRAKE: Is that a fair assessment? Dr. Weiss? I see that is not enough; right.

DR. WEISS: Now, that is helpful. When we get beyond the letter questions, if there is a recommendation for market approval from this committee, we have several questions about what populations it should be indicated and studies in other populations.

But one of the questions, and we have had experience with these kinds of studies in other therapies such as anti-TNF strategies where the question specifically is if you have an adult who is being treated on a chronic basis, and they are coming in for their yearly flu shot, is it important to have a study, and these studies can be done in a controlled fashion, to determine whether or not these individuals actually can mount or have a blunted response to the standard vaccinations that they might be getting while they are on treatment.

DR. DRAKE: Thoughts on that question?

DR. SWERLICK: I think it might be helpful to interject any previous experience you have with the anti-TNF biologics if those answers are

appropriate to questions that are being posed here. In particular, actually, I was thinking about the previous question about repeated courses. How has this been handled before and what was the justification for those criteria?

I think that is really useful information.

DR. SWERLICK: I think for both anti-IL2 receptors, anti-CD25 products and anti TNF-receptor products, we have rather routinely had, I think almost invariably had, postmarketing commitments to study the impact of those on vaccination of recipients. I am not sure I could generalize what the results of those studies are. There is some controversy in some cases.

DR. DRAKE: Seth?

DR. STEVENS: I think that some of my hesitancy is when we talk about moving the use of this drug to different populations and the task before us today. So in terms of not an increased risk of influenza in the patients that were treated with this drug to date, those sorts of things give me a certain perspective. Then when you start saying, well, what about elderly people who should be getting these vaccines that were not specifically studied, that is where I start to lose

my solid footing.

So I guess I just have that as a comment, not to sort of derail things but I think that I have agreed essentially with what we just heard from the FDA and from the other committee members.

DR. DRAKE: Dr. Taylor

DR. TAYLOR: Do a small study. Figure out what is going on.

DR. DRAKE: You want to do a small study, figure out what is going on. Premarketing? Postmarketing? Or either?

DR. TAYLOR: Either.

DR. DRAKE: So that gives you some flexibility. I have a question about lymphocytes. Somehow, I still haven't got it about the potential nonrecovery. It seemed like there was a small percentage of patients who never recovered. This is one time I am going to ask Dr. Seigel, perhaps you can help. If not, then I am going to go to the company because I am still confused about how important an issue is that and what must we do about this recovery, and is it important.

DR. SEIGEL: I will defer, actually, to Dr. Marzella but, except to briefly summarize, as I understand the data, a lot has to do with how you

define recovery. If you talk about recovery to the lower limit of normal as opposed to recovery to baseline as has been pointed out, that will differ.

Over a period of nine months, there is not, in aggregate, a recovery to the pretreatment levels, whether those depressions are clinically significant and what level of recovery is important. Lou, do you want to add to that?

DR. DRAKE: Maybe we are knocking out the bad guys that need to be knocked out anyway and hopefully they will recover with more normal lymphocytes. How is that for doing a short cut?

DR. SEIGEL: Not bad.

DR. DRAKE: You know what I am trying to say.

DR. MARZELLA: I guess you are either an optimist or a pessimist or you want to see the data before you make a decision.

DR. DRAKE: Thank you, Dr. Marzella. That is just terrific. We have really clarified this issue.

DR. MARZELLA: I think that, obviously, it is a profound biologic change. To be honest, the clinical significance is not known, but that doesn't mean that we don't need to follow these

patients and document when, in fact, a recovery occurs.

There is similar experience in other indications. For instance, we have seen other products that cause lysis of T-lymphocytes that cause profound depressions. It takes sometimes years for these counts to recover. We still don't have the full picture of what it means but I don't think we can afford to ignore it. I think that we need to understand what happens.

There is a suggestion, at least with two cycles, that these decreases can be cumulative. It will be important to clearly understand whether they are or not. So my sense is that they need to be followed.

DR. DRAKE: I would ask the committee--I agree with you on that, actually. That is my sense. The question is is this important enough to be done preapproval or postapproval. Does the committee have a sense on that? Is this something that can be done after approval to follow it out or does it need to be done ahead of time?

DR. ABEL: I think it depends on the number of cycles these patients are going to be receiving.

DR. DRAKE: No, no. That is not the question. If we decide to approve it, they will be receiving cycles.

DR. ABEL: Well, that's true.

DR. DRAKE: So that is not the issue.

DR. EPPS: I think it should be done before. Most of these people have only had two and they still haven't recovered. That is just my feeling. I think we need more data.

DR. DRAKE: We just heard Dr. Marzella say, and I am not being argumentative. I am trying to be a little bit of a devil's advocate. We just heard him say that sometimes it takes years for us to figure this out. In terms of risk-benefit, do we want to deprive--if we decide this is efficacious, do we want to deprive patients of this drug?

DR. EPPS: At what risk?

DR. DRAKE: At what risk? I don't know. That is the question I am posing to you guys.

DR. MARZELLA: If I can make another comment. Another option would be to reconsider the thresholds that one allows patients to decrease to. That could be also tailored to specific populations, some that are more susceptible,

obviously. So there are different ways of approaching this.

DR. DRAKE: That is actually a very good suggestion is modify the level that you allow them to decrease to so that it is not particularly dangerous so if it continues to go on, you have got a little give room in there until you collect further data. Is that what you are trying to say?

DR. MARZELLA: That is one option, I think.

DR. DRAKE: That is one option. Good idea. Seth?

DR. STEVENS: I would just like to say that that was part of where I was coming from with my question this morning about the relationship of these picking 250 versus 300 cells. I guess, just to balance Dr. Epps, I would be inclined to say that those studies could be done after rather than before because--for a long list of reasons.

DR. DRAKE: A sense of the committee. How many think it could be done before? This is just a sense of the committee. I am just going to have them hold their hand up so I can kind of get a sense. I am not getting by name at all. I am not voting. I just want a sense.

Who thinks they can be done afterwards? Okay; we are getting somewhere, then. That's good. I hope you guys recorded that the committee split but it seemed to me the sense was that--I am going to restate it. The sense is that there are some members of the committee who feel it should be done premarketing but there is a greater number of the committee that thinks it could be done postmarketing.

But I think you are getting a sense that there is a high level of caution that should be exercised in this arena and certainly very careful follow up and perhaps periodic reviews, maybe even back before this committee sometime in the future or back before the FDA, certainly, within a rational period of time because I think the risk is nobody wants it to get away from us because we are uncertain about what we are going to see with repeated cycles.

Is that a fair expression? Is that a nice summary of where the committee is? Dr. Epps, you don't agree. Feel free to speak up.

DR. EPPS: I am just listening.

DR. DRAKE: Okay.

DR. SWERLICK: I have a question. Is

there any data that would suggest that the average T-cell count, CD4 count, seen after the infusion which is within the normal range confers a risk of infection to any population?

DR. DRAKE: There is no evidence of that that we have been presented.

DR. SEIGEL: That CD4 counts such as were observed here confer risk of infection to other populations in other settings?

DR. SWERLICK: Yes.

DR. DRAKE: That statement was made that both the sponsor and the FDA were in agreement on that during the presentations.

DR. STEVENS: I guess I would just raise the issue that entity that was popular several years back of idiopathic CD4 lymphocytopenia in which there were opportunistic infections and malignancies that were associated with low CD4 counts that persisted in the absence of HIV and so on.

That would be the only other instance that I could consider.

DR. SEIGEL: I think not all CD4 lymphocytopenia is the same. In most cases, you are going to have functional disturbances.

Sometimes, you have clonal deletions. Sometimes you have selective memory or naive, depending on the drug and the disease. So I am not exactly sure how to approach that question.

DR. DRAKE: The Chair has recognized Dr. Krueger.

DR. KRUEGER: I would like to make two very brief comments. The first is I have, in a study of effects on memory cells, subsetted the memory-cell effects into long-term memory which are called central-memory cells and then other cells that are called peripheral memory cells which are the bad guys, if you will. They are the short-term effectors that end up at the skin and produce psoriasis.

There is a relatively small effect of this drug on decreasing the number of the long-term memory cells. Instead, the effect is mainly in this short-term expanded population. That, to me, gives some comfort in the idea that long-term memory is not being abrogated. But my studies are limited to a single course and don't address the multiple-course issue.

Secondly, I want to say that there were studies done in England with an antibody called the

CAMPATH antibody many years ago which was profoundly T-cell-depleting and produced T-cell counts that were regularly below 100.

There were, in that setting, some immediate concerns with infection seen but there has actually now been many, many years of follow up of patients that have stayed regularly with T-cell counts below 100. In that setting, while there is some risk, it is clear that it is a very different risk setting from the AIDS population where the T-cell risk below, let's say, 250 or 200 cells is quite high.

So I think the risk of immunosuppressive for an individual T-cell count really depends on the circumstance.

DR. BONVINI: Dr. Krueger, could you please state--I haven't seen the result of this study that you have referred to now. Is this derived from in vitro experience, in vivo, and if these were patients, how many patients are involved in the calculation?

DR. KRUEGER: May I have the Chair's permission to show a slide?

DR. DRAKE: Yes.

You notice how he just happened to have

that at his fingertips?

[Slide.]

DR. KRUEGER: This is a measure in twenty-one patients that are treated with alefacept with the intravenous administration at the standard dose. So this is the effect on these two groups of cells that are called central memory and infector memory. The overall effect on memory CD4s is about a 30 percent reduction. What you can see is that this long-term memory group is affected much less than this and the p-value for this difference is incredibly--

DR. BONVINI: Based on CCR7?

DR. KRUEGER: Based on CCR7 and CD4 who have RA negativity as well as a lineage marker. It was a four-color flow experiment. There is a fourth antigen in this. So these are actual in vivo data for psoriasis patients treated with the drug.

DR. BONVINI: Were these responders, patients--

DR. KRUEGER: This is a mixed group. I will tell you that the responding patients tend to have more depression of this group of cells compared to nonresponders but that, in the

nonresponders--I'm sorry; this differential is extremely well preserved.

DR. DRAKE: Dr. Katz?

DR. KATZ: I have a sense in our discussions on the last two points that there is some anxiety about the safety. If that is the case, why need this be rushed without gathering more patients? We are talking about 1,000 patients. We are talking about multiple courses of how many patients, 300 patients.

It is a definitely effective drug but I don't see the urgency before they gather--if there is a little uncertainty with many more patients, then that would be more valid to take the risk. But, otherwise, we are dealing with small numbers and anxiety around the table. The question is everybody is talking about labeling and follow up and so forth. Don't you think that that should be done before it is released?

DR. DRAKE: Dr. King?

DR. KING: I guess if you take it in context, I tend to think biologics and chemicals like methotrexate are two different things. Insulin has been around a long time. It is a biologic. Growth factors for the hematopoietic

disorders, and so forth, are biologics. So there is a great deal more information than you would think out there.

This is building on that, not starting de novo. So when you think about this product, you are really talking about there is not any known effect on the liver or the kidney. So now you are talking about what is the effect on the immune system which is what it is targeting. It is not going to target the central nervous system or the liver or the kidney. What you are really talking about is what is your long-term risk for an infection or cancer or whatever.

I have the bias that, basically, skin cancer starts for most people in childhood. So you are not literally going to survey cancer effects for a long time except in a registry-type study.

So if those of us who are diabetic waited for a long time until we got total risk issues on insulin, most of us would be dead. So I am comfortable with a registry as long as we define what we are measuring and I haven't heard anything here to tell me that infection was up or cancer is up. All we really had a potential bogeyman of what it may or may not do.

DR. KATZ: There is a little, not statistically significant data, but there is a little direction on most cancers and infections. This is really not analogous to hormone-replacement therapy. You are interfering with immune response. Hopefully, this is going to be completely safe and it will afford the 10 to 25 percent of patients over placebo with effective treatment, but I am just saying that, perhaps, more patients should be treated.

DR. KING: Actually, I beg to differ with you because I don't think of any difference between a cytokine and a hormone. The immune system releases peptides and peptides hit receptors and that is how hormones work, at least the peptide hormones work.

DR. DRAKE: Seth?

DR. STEVENS: I think we are back to the question that Dr. Swerlick asked to start us off which is how safe is safe enough. I think if we repeated all the studies and we doubled the length that they were followed and doubled the number of cycles, maybe the statistics would shake out and maybe they wouldn't.

But I think we are looking at shades of

gray rather than eventually reaching black or white.

DR. ADELMAN: Madame Chairman?

DR. DRAKE: Yes.

DR. ADELMAN: Would it be possible for me to put up one slide that just might help focus on this conversation?

DR. DRAKE: Yes.

DR. ADELMAN: We recognize the challenge and the concern about how much data are necessary to approve a fundamentally novel drug in an indication that has significant need. As some have said, how much data is enough? You never really have enough. That is why, in the context of our conversation, we have discussed our commitment to going forward with a very structured organized registry or trial after approval that we would envision would collect thousands of patients and carefully monitor their long-term outcome from safety and focussing on some of the key issues that have been raised today which are absolutely correct and relevant for concern.

But what I want to do is just point out that the process continues even today as we speak because there are 800 patients who are in various

stages of retreatment. The serious adverse events we hear about immediately when they occur. So I think that this slide, as of May 20th, so this is current--you can see that right now, up to Course 5, we actually have 116 patients currently receiving their fifth course of therapy.

The number of serious adverse events is listed here. You can see that there are serious adverse events that occur at all courses, but we haven't seen anything new or unusual that we haven't discussed today, and the trend is not toward increasing incidence of serious adverse events.

So we feel that this process is ongoing. The agency is being made aware of this information. They will be made aware of the information up to and through an approval date and we will probably expand the size of this group that we are following.

But this is the core group to address the question that has been raised which is how safe is multiple treatment. These patients are undergoing multiple treatment and we are carefully monitoring their lymphocyte counts, incidence of infection, incidence of malignancy and any other untoward