difference whether you get something different in terms of especially time to healing as a parameter, but that's neither here nor there.

So could we -- Henry.

DR. LIM: Yeah, to address what Dr. Wilkin had mentioned, my feeling is that there is enough difference between the .1 and .03 for the adults to make a clinical difference.

DR. TANG: Yeah, I was going to say there was a slide presented in the morning. This is a way to interpret the inaccuracy, interpret the data for the subsequent analysis. So you rarely for the .1 and .3 for the moderate -- it depends on the baseline disease severity classification. For the moderate there wasn't any difference.

But for the severe group, the difference is 19 percent versus 35 percent. I wonder what the P value for that subset analysis is.

ACTING CHAIRMAN STERN: That was significant.

DR. TANG: To what degree?

ACTING CHAIRMAN STERN: I think it was

.04, is my recollection from the morning.

DR. TANG: Point, oh, four?

DR. LAWRENCE: Do you want us to show that again?

ACTING CHAIRMAN STERN: Wasn't it .04?

DR. LAWRENCE: No. We can show that again.

ACTING CHAIRMAN STERN: Yeah, would you? This was severe adults, .03 versus .1.

DR. LAWRENCE: It's .009, the statistical significance.

DR. TANG: Oh, oh, nine. But that's a .01 difference.

ACTING CHAIRMAN STERN: And overall in adults it was?

DR. LAWRENCE: Point, zero, four.

ACTING CHAIRMAN STERN: Okay. I'm glad I didn't remember.

DR. LAWRENCE: I'll stand up. I'm sorry.

When we combined the two identical trials in order to get some better power, what we show -- and if you could show that slide as well. I showed it

this morning -- when we combined the two adults together since they were identically designed trials, you can see, again, the two adults. There's the .04. That's the one you remembered earlier.

ACTING CHAIRMAN STERN: I'm sorry.

DR. LAWRENCE: No, that's fine, and then the other was the severe, .009.

ACTING CHAIRMAN STERN: But as I mentioned earlier, I found Dr. Okun's subset analysis where you think of everything as a coin toss between each subgroup, which were the logical subgroups to really look at people in terms of clinical and patient characteristics, where I believe there were only two of those many comparisons. One was children and one was females where the differences did not go in the same way.

There were two or three slides that Dr. Okun showed which I found in some ways as persuasive as the other.

DR. TANKS: So you think there is some evidence.

DR. LAWRENCE: Excuse me. We just have

one more slide that speaks to this issue, if we could show it.

Is that the one you wanted to show, Bill?

DR. FITZSIMMONS: Just to further elaborate on this point because the treatment difference was something discussed, we've just looked at the overall adults in the ten percent difference; this severe disease, which had the 15 percent difference; and then if you look at the extent of body surface area involvement, there is a 25 percent difference between the two concentrations.

These, again, were very consistent across our adult studies. These analyses, the concept of looking at severe as well as body surface area actually were predefined, again, in the protocol. So these were important subsets that we wanted to evaluate and are consistent in their treatment difference and increasing difference between the two concentrations.

ACTING CHAIRMAN STERN: And it look like you did nine in the 35 and 36, the adults. You did nine subgroups, and it was nine times that the higher

concentration won.

DR. OKUN: That's correct.

ACTING CHAIRMAN STERN: And I seem to recall that if you flip more than six times it's significant and always comes up heads. That's my recollection.

(Laughter.)

DR. TANG: That's exactly what we're trying to get at: how small the P value is. Yes, because if it's .0001, that might tell you some different story.

ACTING CHAIRMAN STERN: Well, nine flips in a row is pretty small.

DR. TANG: Yeah.

ACTING CHAIRMAN STERN: So should we have a vote? Would someone move as to whether -- I'm sorry. Would someone move and we can vote obviously either way? Is there sufficient evidence for superiority of .1 to .03 in adults? Does someone want to?

All those who believe that to be the case, please raise their hands.

DR. TANG: This is in?

ACTING CHAIRMAN STERN: This is in adults, that there's significantly more effectiveness in adults of .1 over .03; that there's evidence for significantly greater efficacy.

That's not to say that it is better in terms of risk-benefit or anything else, but just that there's evidence that it works better given the evidence base.

(Show of hands.)

ACTING CHAIRMAN STERN: It makes me nervous when the biostatistician doesn't agree.

(Laughter.)

ACTING CHAIRMAN STERN: And how about the same question in children? All those who believe that there is reasonably robust evidence that .1 is superior to .03 in children, that they're comfortable with that as significantly better, again, just in terms of efficacy, not in terms of risk-benefit. All those who believe that to be demonstrated?

(Show of hands.)

ACTING CHAIRMAN STERN: Okay. So I'll

take it that that's not shyness but -- so the answer is I think we think the adult case for a difference in efficacy is reasonably robust, and the childhood case, there is a lack of that evidence.

Now we come to the hard things. Has the safety profile of Protopic in the treatment of atopic dermatitis been adequately determined for unrestricted chronic therapy as first line therapy?

And I would like to ask Dr. Wilkin and perhaps the sponsor, as well, to define "chronic" and to define "first line."

Dr. Wilkin, please.

DR. WILKIN: Well, chronic I would say in general means not acute.

(Laughter.)

DR. WILKIN: Whether it actually implies that it's continuous chronic or intermittent chronic, we don't really have anything in the CFR that helps us -- Code of Federal Regulations -- that helps us with this distinction, but I do know that in some literature areas and in some pharm. tox. areas one view has been that if one will have a cumulative of

six months' exposure over a decade, that that would be considered a chronic kind of therapy.

ACTING CHAIRMAN STERN: Did you want to comment on that one?

DR. LAWRENCE: Well, I think it is very difficult, and I think, again, the differentiation as we tried to point out in our response, as well, is that we are not implying this for continuous use. It really is the intermittent use over, you know, a prolonged period of time. Certainly this is a very lifelong or certainly prolonged disease, but again, with intermittent treatment, not continuous therapy.

ACTING CHAIRMAN STERN: Elizabeth?

DR. ABEL: I would suggest amending the question to say for unrestricted therapy as a first line treatment for chronic disease because that perhaps would be easier to answer because patients might not necessarily be treated continuously for that year or am I not getting that right?

I have a question because we are told that they relapse promptly after stopping treatment. So does this imply that patients are continued daily for

the whole year or could they be treated intermittently?

ACTING CHAIRMAN STERN: I think this implies intermittently, but on a long-term basis through multiple exacerbations and also when the disease is percolating along.

DR. ABEL: I think the question the way it's worded is a little confusing because it's first line treatment as a chronic disease, but it may not be necessarily unrestricted chronic therapy. So maybe that first chronic could be deleted and substituted.

ACTING CHAIRMAN STERN: And even more, I'm interested in what does it mean to be a first line therapy.

DR. WILKIN: Well, I do like your notion of long-term intermittent might be a better expression than unrestricted chronic. i mean, I think that would be a nice exchange.

First line treatment, I think, in general to me means that if someone comes in and they have fairly uncomplicated atopic dermatitis that might respond to a variety of things, that this would

nonetheless be used. That would be first line.

A second line would be where you've tried a lot of different agents or at least several agents, and you really haven't been able to achieve control. We understand that atopic dermatitis is a chronic relapsing kind of condition. It's more of the notion of can you achieve control with some other agent, perhaps one that we have a longer understanding of the safety profile before one would go to this treatment.

Does that --

ACTING CHAIRMAN STERN: I wanted to clarify that because I took that as you do with some of, for example, agents in psoriasis. It says for people who are intolerant of or nonresponsive to A, B, and C therapies. This is to go, and I guess my feeling about any new agent for a chronic disease that is likely to be used intermittently over long periods of time, that until we have a bigger database, to me it doesn't imply in any way an inferior therapy, but the logical communication to give to clinicians is: use this when the agents that have been around for 30 to 60 years are unacceptable to the patient, no long

effective at least at that point in time, or there's a counterindication to the use because of side effects the patients already experience, the location of the disease, et cetera, et cetera.

And I myself would be uncomfortable with first line in that you shouldn't think about the devils you know before the devil you don't know quite as well in terms of -- and that's not meant at all pejoratively -- in terms of your experience with the agent and in terms of a really very extensive safety and side effect profile which needs to be developed.

So I guess what I would say with that is that I would be much more comfortable with some kind of phrasing very comparable to what you do for some of the more -- for certain of the agents for the treatment of psoriasis, where you imply that it's for people who are no longer being helped by, intolerant of, or there's some counterindication for the more standard therapy for atopic dermatitis.

And I guess the other thing in there is although we've always talked about it, to me there's a bit of a difference. One of the problems, it's very

hard to define what's mild, moderate, and severe disease, and certainly the intervention and how quickly you go to something with severe disease, some individual with severe disease, how quickly you go to an agent like this is very different than in moderate and even more different than it might be in, quote, unquote, mild disease, where it might be an appropriate -- and I know the company's not looking for mild disease as an indication, as I understand it.

DR. LAWRENCE: Our studies were conducted in patients moderate to severe.

ACTING CHAIRMAN STERN: But there may be some differentiation in our recommendations about severe versus moderate disease, as well.

DR. SIMMONS-O'BRIEN: The company suggested that it be used until clear and then go beyond that times seven days, and at the same time we've been made aware that as soon as the individuals are off treatment, they flare.

So my question is: what would be the recommendation for the interval free period or the holiday period for this medication? It seems like

it's going to always be needed.

DR. LAWRENCE: If I can clarify a little bit, the average time in our long-term studies to recurrence was about a month and a half to two months. So it wasn't an immediate recurrence. The period of time that we actually evaluated patients during the pivotal trials was a fixed two-week period by design, but that's very artificial, and that accounted for about 40 percent of the patients that did have some recurrence, although less severe disease.

In the long-term studies the average time to recurrence was a little bit longer. I believe it was about 54 days, 55 days. So there is a period of time during which the patient does not recur, has a much less severe disease.

ACTING CHAIRMAN STERN: But I probably once more misremember, but I had thought that you had said in the one year study the average duration of days on use was something around 280 or 290 days.

DR. LAWRENCE: Yeah.

ACTING CHAIRMAN STERN: Which would be incompatible with people being clear for four or five

weeks. So you're saying recurrence in a prior treated area, but --

DR. LAWRENCE: Yes.

ACTING CHAIRMAN STERN: -- this is really supposing continued use essentially 80 percent of the year in these selected individuals.

DR. LAWRENCE: Well, it was actually -- and it's very confusing. The average length of time on the therapy was 279 days. Most patients chose to use continuous therapy, and we permitted them to do that because we wanted to get long-term, at least 12-month data.

The recurrence data comes from those patients that discontinued therapy during the course of the trial. That accounts -- there were only several -- there were, I think, 45 or 50 patients that actually did that, and those are the patients upon which we based our recurrence data.

So there's a little disconnect there, but it really is true, true unrelated almost, one of those things where you do have two separate sets.

So in those cases that did discontinue, it

was about 54, 55 days to recurrence, but many patients chose for their own purposes, as well as the physician, to continue long term, and in this study where we were trying to get a prolonged, continuous exposure to gather data, we did permit patients to do that, although as you noticed and as I showed, most of those patients did have improvement both in the amount of body surface area treated, and the amount of ointment that they were using. So it was still continuing to go down.

DR. LIM: I would like to come back to the issue of the first line therapy. In your previous response, Dr. Lawrence, you did mention that most of the patients were in therapy, in fact, were on study, in effect, have been on other therapy. So probably by definition those patients are -- you are not using the medication because the study design is such that those patients are not using them as first line therapy.

DR. LAWRENCE: Well, I think with regard to that question, Dr. Lim, certainly the majority of the patients, and especially the patients who were older, had had previous therapy, and in fact, most of

those patients had, as you've heard, I think, very eloquently from the patients, failed numerous other conventionally, currently available therapy. That is correct.

ACTING CHAIRMAN STERN: I guess this might be a point to actually when we think about intermittent long-term therapy and are thinking about safety profiles to realize that we have at most one year of data on a bit more than 1,000 patients in each category, and I guess one of the things is that one has to always look at this is a living, evolving thing, and I know that the company said that they don't think this is over, but perhaps part of it might be that we believe -- changing this to we believe that there's reasonable evidence for safety for one year of intermittent therapy, and that we believe as time goes on Phase IV, other studies mutually negotiated between the sponsor and the FDA to address the issues of long-term safety are the only way we'll know what really happens after a year.

And I'm much more comfortable limiting our recommendations to what we know, which is a year, and

saying we feel good about beyond that, but we'd really like to see data rather than just feeling good about it.

DR. LAWRENCE: I think that's very eloquently stated, Dr. Stern. In fact, we acknowledge in our presentations earlier that our long-term studies have been for periods up to 12 months or one year, whichever is easiest to write in the label clearly, and we acknowledge that additional post marketing studies are valuable, and that was certainly as part of our final comments -- I think that is where Phase IV becomes very valuable.

ACTING CHAIRMAN STERN: Joel.

DR. MINDEL: I distinguish between the complications of topical corticosteroids and systemic, and in evaluating this drug, I would like to see it approved as a second line drug after failure of topical corticosteroid. A judgment as to whether oral corticosteroid, I think, is a better or safer drug you can argue, but my understanding of topical corticosteroid in relation to what we know about this drug, I'm more accepting of that type of labeling.

ACTING CHAIRMAN STERN: I guess my own clinical opinion, and not being as expert as that, in comparison to systemic steroids for this disease, at least in one year of use to me this seems like a much safer drug, but in comparison to topical steroids, I think, you know, it took people who treat a lot of psoriasis a long time to formalize the obvious, which one of the things in managing chronic diseases is to think about trying to alternate between therapies that have different side effect profiles, different concerns, and that, in fact, you may in the long term minimize long-term toxicity by using one agent for a while and when a person is either doing better or not doing as well with that agent, switching them to another agent that has a longer safety profile or is less expensive or whatever the reason is.

So I think we're really talking about how to integrate something into a therapy that will in any individual change very much over time. I mean one issue we haven't heard about actually is, occurred to me as things change over time, safety in pregnancy. I haven't heard any data, and I'm sure you have a

large database, but could you tell us in 20 words or less what about in organ transplants?

DR. LAWRENCE: I can with two statements. The first is that tacrolimus systemic has a Category C, which we have requested for this agent as well. We did have several cases of pregnancy during the Protopic trials, although we preferred patient not become pregnant, and in those cases it was very variable.

Patients in the vehicle group did have spontaneous abortions. There were also several normal children born to patients on the .1 percent tacrolimus. So I think that the issue on pregnancy is that there's very little data, and we feel comfortable with pregnancy Category C at the present time, which we have submitted.

DR. MINDEL: Just along those lines, the mother that puts the ointment on the two year old skin is being exposed to the ointment, and if she's pregnant, she also is -- just an observation -- she also is being -- exposing the fetus to the ointment.

ACTING CHAIRMAN STERN: I think one of the

fortunate things about this agent is that one reason it may work so well in atopic dermatitis, and it's my understanding from published literature that if they didn't have the same success, for example, in psoriasis, that in atopic dermatitis you have an injured barrier, and unless you have eczema on your fingers, when it will be therapeutic for that, there's no better barrier except the bottom of your feet than the tips of your fingers.

So I think the degree of systemic absorption, especially, is likely to be very limited if you use one or two fingers and don't use the back of your elbow to apply it to your child.

(laughter.)

DR. BIGBY: This is sort of basic clinical trial stuff, but that sentence, "the safety profile of protopic in treatment of atopic dermatitis has been adequately determined," I think, it's clear that, you know, randomized controlled trials are not adequate to determine the safety of anything, especially for, you know, relatively rare, but serious toxicities.

And there are legions of drugs that were

deemed to be safe on the basis of, you know, premarketing data, benoxiprofen, phen-fen. You could do millions of these, yeah.

ACTING CHAIRMAN STERN: I mean, I think that's what I sort of implied in talking about we really need data, both longer term and in larger populations, and especially in those populations that we might be most concerned about, and that's, I think, something that the agency and the sponsor to figure out perhaps with our advice at some point about what are the issues and what are the designs.

DR. WILKIN: I think that's actually right there with the spirit of this question. We're really not asking is it safe. We're asking has the safety profile been adequately determined. Are there glaring lacunae in the safety database, something that would need to be known before chronic therapy or before first line or these sorts of things?

And if so, then you'll have an opportunity in Question 5 to tell us what kind of studies will generate what kind of information for labeling

DR. SIMMONS-O'BRIEN: Just to also throw

out there, I'm also concerned that when we agree that something can be first used as a first line treatment, that there's a potential for abuse of any particular drug, and we want to make sure that if this drug is approved, that the people who really need it are the ones who get to use it, and that it's not handed out like candy, and a lot of the leg work that should be done in, say, evaluating potentially a child who has, you know, limited to even moderate atopic eczematous dermatitis who might just totally clear, and there are some that do, if you find out that they have potential allergens that are causing their disease process, as in what they're eating or the environment and their house, that we're somehow not going to shortchange those children who could be remedied in other ways because there is a new panacea, so to speak.

ACTING CHAIRMAN STERN: I mean, that -- I agree with you completely, and I really think in terms of recommending labeling to say that something is for people who are refractory to or there's counterindication for conventional therapy, particularly in this disease, topical corticosteroids,

either because of the nature of the patient, the location of the disease, to me is a reasonable way to start with a drug that there's going to be, if anything, a great push for wholesale adoption, and what we'd really like is adoption in those individuals where we know the benefit is high compared to the alternative, and therefore, a slightly undefined risk profile still makes us comfortable with its use.

And I don't know if the company is -- how the company feels about having it, you know. First and second line implies either -- implies a ranking as opposed to a logical ordering of treatments within an individual.

DR. LAWRENCE: I think your points are well taken, Dr. Stern, certainly with regard to the issue of how it is positioned, the armamentarium, and what decisions the physician needs to make to enroll the patient, and I certainly agree with the other physician as well in her comments.

I think that we are certainly very prepared to work with the agency to really define as clearly as we can with obviously your recommendations

as a committee on how to really define how this drug should be utilized.

We believe it offers a very important therapeutic option to physicians, and I think part of our goal as a company is to insure that we provide those physicians with the proper information on how to best use this agent to make patients improve.

DR. ABEL: Rob, an additional comment. Regarding chronic, I feel uncomfortable voting on such an unrestricted question, open ended rather, and I would like to strike the "unrestricted."

Let's see. The treatment of atopic dermatitis has been adequately determined for -- oh, okay. You've changed it already. I didn't even see that. Okay.

And I also agree with the first line, that we should strike the first line and maybe it is. No, it hasn't been stricken yet. So I would like to also echo that I think we should be in "recalcitrant atopic dermatitis" or something and not "first line."

ACTING CHAIRMAN STERN: Perhaps something along the line of moderate/severe atopic dermatitis

not responsive to conventional therapy.

DR. ABEL: Something like that.

ACTING CHAIRMAN STERN: Or where convention therapy is counterindicated.

DR. EPPS: Can I just make a comment? My concern would be more as an advocate for the younger children. Those are the ones that I see all the time. The stories that we heard today, and I certainly have a lot of empathy for them, are stories I hear every single day.

A lot of the kids are generalized. It's not, you know, 100 square centimeters or even 500. It's all over.

The younger kids perhaps not only will have increased exposure to the medication, but will also have an increased lifetime exposure to ultraviolet light, which relates to some of the potential side effects.

Also, someone presented that they had higher levels on day eight versus day one after absorption versus adults. So that should be taken into consideration, too.

And I would like to echo Dr. Simmons-O'Brien's comments that this is a multi-factorial disease. A lot of parents looking for the magic bullet or the magic drug to get relief, and certainly there are people who definitely need this. Believe me it would make my life and a lot of people's lives a lot easier.

However, we want to make sure that it's safe and indicated.

ACTING CHAIRMAN STERN: Any other comments or questions by the committee?

We're changing the question in terms of as a --

DR. ABEL: One other question. Why not limit it to one year?

ACTING CHAIRMAN STERN: Well, I guess my reason for that is knowing how Phase IV studies go, there's not going to be -- it would be impossible in a year from its approval to have data on more than one year. So you have to have adequate lead time.

You know, we're not going to have anymore information, assuming the drug were magically approved

tomorrow and on the market the day after tomorrow. A year from now we're not going to have any more information about long-term safety than we have today, safety beyond a year.

DR. ABEL: There are other drugs on the market that are approved for use up to one year, and I wonder if that might encourage physicians to use it more judiciously and intermittently rather than continuous, long-term use if they know its safety profile has been established for up to one year because over one year we don't know.

ACTING CHAIRMAN STERN: I guess my preference would be to share the information about the limits of our knowledge in terms of long-term safety, but not limit the individual physician to a year because then you're really in a Catch-22 for patients for whom the agent is clearly effective and helpful, and you've now treated them for 14 months, and there are no additional data.

And if it says safe up to a year, that's different than to say our database is up to a year. You know, we're operating with less certainty about

safety both in terms of rare side effects, as Michael has indicated, which there's no power in studies of a couple of thousand patients to detect, and also in terms of very long-term, intermittent use.

But I think telling people what we know and not saying, oh, because we don't know it, that means it's not safe; I mean that's just my own feeling.

DR. ABEL: I didn't think we were saying it's not safe after one year. It's just that we don't have data beyond one year for determining the safety profile.

ACTING CHAIRMAN STERN: So you would just put in essentially the safety not in terms of limiting the use to one year. Oh, okay. I misunderstood you. I'm sorry, but you would just put it in the safety information.

DR. ABEL: Yes, that has been studied up to one year.

ACTING CHAIRMAN STERN: I think that's usually pretty routine.

DR. ABEL: But we don't really know.

ACTING CHAIRMAN STERN: Isn't it? That you say in X patients over Y period of time?

DR. WILKIN: That's right. We try to put that database in there for exactly the reasons as you describe. It's hard to, when crafting the labeling, and the sponsor, of course, does a lot of the crafting of the labeling, and their insights are important, but in the end it's hard to anticipate every single patient that is going to come into the dermatologist's office and the different aspects, different factors that they'll bring to the clinical decision of whether to use this therapy or which concentration and for how long.

So it's important to allow the clinicians to make the important decisions at the bedside.

I think the question, again, is, you know, close to the spirit of this, which it's the safety profile question. I mean it's not is it safe. It's do we know enough about the safety for this kind of indication, long-term, intermittent, first line treatment.

DR. EPPS: There weren't any trials

comparing it head to head with topical steroids?

ACTING CHAIRMAN STERN: I think there were European trials comparing it head to head, but they weren't presented.

DR. EPPS: These were all vehicle.

DR. LAWRENCE: Yeah, in the U.S. we used vehicle to control paradigm.

ACTING CHAIRMAN STERN: Right.

DR. LAWRENCE: There were two studies in Japan that were very short-lived. One was a one-week study, and one was a three-week study that were -- I believe those were included in the briefing document both from Fujisawa and the FDA.

We did show comparisons to aclamethazone on the face and showed superiority with tacrolimus ointment, .1 percent, and with beta methazone valerate on the trunk and limbs for a three-week treatment again with a numerical advantage with tacrolimus ointment, but in equivalence with regard to efficacy, but again, those were very short, open label studies, and we have not conducted any head-to-head to studies here in the United States with that, and we don't have

any data that we are ready to prepare to send to the FDA at this point.

ACTING CHAIRMAN STERN: Henry.

DR. LIM: Yes. As part of the safety, I would like to address again the sun and photocarcinogenesis issue. In terms of the sun avoidance, in terms of the labeling I think it has to be made very clear that the patient needs to do -- to have sun avoidance practice and also need to use broad spectrum sunscreen because, again, coming back to the light source that was used in animals and I understand that in human it may be completely different situation, but it is a broad spectrum light source that is used that contains UVA, as well as UVB.

So the broad spectrum component of sunscreen needs to be emphasize.d

DR. LAWRENCE: and we have attempted to make as best we can some early attempts at that by saying they should practice or not avoid exposure, unprotected exposure to natural or artificial sunlight. I think additional guidance that we could provide to the physician, we would certainly welcome

input on and are willing to talk to the agency, again, about how best to define what that sun protection should be.

ACTING CHAIRMAN STERN: I guess I have two issues about that. One is my experience with people with atopic dermatitis on the face is that unless they're willing to use essentially physical barriers, sunscreens, that most people can't tolerate the sunscreens; that it kicks up their eczema. So you're sort of, you know, between the devil and the deep blue sea.

The second is clearly the risks are going to be dependent on the phenotype of individuals, and the recommendations for someone who is fair skinned and blue eyed is very different than someone who never sunburns and is deeply complected.

The third is at least based on -- I always worry about children a lot -- but based on data, I'm most worried about actually people who have already had prior substantial sun exposure, people who sort of look like me in terms of using it as opposed to people -- it's not so much what you're doing this week. It's

what you did ten and 15 years ago with immunosuppressive agents. That is my concern about skin cancer risk.

And clearly, it's also for those very same reasons very anatomically dependent, and to me this is one of the tricky issues which I think we'll get to in the next question.

On the one hand, this agent has very substantial advantages over top corticosteroids on the face. On the other hand, if you're looking at about one of its two potential long-term toxicities, it doesn't happen anywhere more often per square sonometer or with, in fact, more impact on the individual because of disfigurement than on the face, except for the bald scalp and ears of older men, where it's particularly dangerous.

DR. LIM: I just wanted to comment on a comment that you made. I think it is true in terms of photocarcinogenesis is very phenotype dependent. What I'm not as certain is whether photocarcinogenesis in the context of immunosuppression, whether it's enough data to say that skin Type I individuals are more

susceptible compared to skin Type VI individuals, are there good data to indicate that?

ACTING CHAIRMAN STERN: Well, the data, at least as I read them, is that the relative risks go up about the same for all groups, but since people who are skin Types IV and above have much lower baseline risks, their absolute risk is much lower.

So, yes, you may in quite low risk populations. You get relative risk increases of 50 to 100-fold, but that's still not a lot of tumors, and in high risk people you get similar increases in relative risk, and you're getting a very high incidence. So the burden of the disease is much greater in those people with innately higher risk.

DR. LIM: Sure, but, on the other hand, for the lower risk individual, essentially they still have significantly increased risk at the same aptitude (phonetic).

DR. ABEL: I'm sorry to get back to this one point again, and I'm going back to the wording of the question again. I would like to propose deleting "long term" since we aren't defining it here, and just

say we're voting on the safety profile of Protopic in treatment of atopic dermatitis as adequately determined for intermittent therapy as a treatment for chronic disease. You could even strike "first line."

So we're asking -- deleting "long term" and just leaving it open ended. And also you could also delete "first line" and you wouldn't have to worry about defining it.

ACTING CHAIRMAN STERN: Shall we perhaps vote? And I think perhaps we should vote dividing this question into two parts. One is as Dr. Abel has suggested, the issue of leaving in or taking out "long term" out of that.

And then the second, the first line because they really are two quite different concepts. So I guess for ease in terms of long-term intermittent, how many people feel that there's a safety profile sufficient with the suitable caveats about what we know and what we don't know and the need for additional information that long-term intermittent safety is as best we can reasonably documented?

DR. ABEL: You could put in there

treatment for chronic disease, and that implies long term. So you could just keep it intermittent, but delete long term only, and then it would be worded intermittent therapy for chronic treatment of a chronic disease, and that implies that it's going to be long term.

ACTING CHAIRMAN STERN: Any preferences on the part of the committee? Someone? Joel?

DR. MINDEL: As long as the term "first line" is in there, I'm going to vote no.

ACTING CHAIRMAN STERN: That's why I say we're only voting up to -- we're talking out first line and now we're only voting about --

DR. ABEL: The first line is still in there.

ACTING CHAIRMAN STERN: I'm sorry. I think what I'd like to do is just have us go up to -- the question is whether we're comfortable with long term intermittent therapy, and then separately discuss whether it's first line or not.

I mean therapy means we're going to talk about some kind of therapy it's indicated for, but it

may not be first line, and I actually prefer -- my preference is long term. So since it's the more difficult one to get by, why don't we leave it there, vote on it, and if not, let's vote to the next one if that's acceptable.

So could be put long term back in there whoever is typing?

(Laughter.)

ACTING CHAIRMAN STERN: So we're now only voting up to long-term therapy, and we're not classifying as to whether it's first line or fifth line or whatever. We're just going up to "therapy."

All those who --

DR. ABEL: Can we have discussion further? Because I'm not comfortable voting on that. I'm uncomfortable voting on long term if it's not further defined. That's --

ACTING CHAIRMAN STERN: Okay. Maybe we should do it backwards. In other words, do what we're talking about long term, and I think I've heard that most people don't believe that it at this time should be considered first line in the sense of, yes, there

should be no difference in your thought process between writing for this versus writing for a Class II topical corticosteroid. Am I correct in that?

You're giving me that look, Michael, you so often give me.

DR. BIGBY: I am not doing looks.

(Laughter.)

ACTING CHAIRMAN STERN: That's what you think.

So I guess I would suggest that we change first line to therapy for moderate and severe disease, not responsive to or where conventional therapy is inappropriate for the patient, or you have those words quite well down for a number of other diseases where there's this similar kind of paradigm.

Can we vote on that part and then get back to the -- are people comfortable with that?

MR. HENRIQUEZ: Let them try to put it up on the screen.

DR. BIGBY: Could you repeat that again?

ACTING CHAIRMAN STERN: For moderate or severe atopic dermatitis not responsive to or where

conventional therapy is inappropriate or counterindicated, some words like that.

PARTICIPANT: Nonresponsive or intolerant?

ACTING CHAIRMAN STERN: Thank you.

DR. ABEL: That phrase "moderate to severe" adequately determined for treatment of moderate to severe.

ACTING CHAIRMAN STERN: Oh, I wouldn't worry about the wordsmithing, you know. I'd worry more about the sense.

MR. HENRIQUEZ: I guess they need it one more time.

ACTING CHAIRMAN STERN: I'm sorry. Not responsive to conventional -- who in the audience said not responsive to or --

PARTICIPANT: Or intolerant.

ACTING CHAIRMAN STERN: -- or intolerant of convention therapy.

DR. ABEL: Resistant, just simply resistant perhaps.

ACTING CHAIRMAN STERN: Yes.

DR. WILKIN: One minor point on not

responsive. They might actually have a response to other therapy, but it might not be --

ACTING CHAIRMAN STERN: But not adequately --

DR. WILKIN: Yeah, it's adequate.

ACTING CHAIRMAN STERN: Not adequately responsive, yes. No, you're absolutely right.

DR. BIGBY: Can I ask a question?

ACTING CHAIRMAN STERN: Sure.

DR. BIGBY: How important is long term and first line to the sponsor?

DR. LAWRENCE: Are you asking me that in the context, Dr. Bigby, of approval or --

(Laughter.)

DR. LAWRENCE: I think that we acknowledge, and in fact, we have talking to the agency already -- I'm sorry. I don't need to knock that over -- that we acknowledge that the studies we have conducted were only for periods up to 12 months, and we fully acknowledge that.

And I think with that concept, as Dr. Abel has alluded to and, I think, Dr. Stern has as well,

perhaps even including in the label that -- and I think this is very nicely crafted as we're working on this -- is the fact that studies involving periods greater than 12 months of therapy have not been conducted.

I mean something along those lines are certainly very reasonable, and I think we would be comfortable with those in the lab.

ACTING CHAIRMAN STERN: Michael, asking the sponsor that is like asking them if they want the 82 left feet or the 99 gallows.

DR. BIGBY: No, no, no.

DR. LAWRENCE: But we do appreciate your --

DR. BIGBY: No, actually I disagree, and I think that the response is right. It's quite reasoned.

ACTING CHAIRMAN STERN: I agree.

DR. ABEL: Could I just suggest a change in order of one phrase --

ACTING CHAIRMAN STERN: Sure, absolutely.

DR. ABEL: -- so that it will read perhaps

-- I can't see it from here and you won't hear me. So I cannot speak into the microphone, but my suggestion would be has the safety profile of Protopic been adequately determined for long-term intermittent therapy of moderate to severe atopic dermatitis.

Now, just switch the of -- has the safety profile of Protopic been, and this whole phrase "in the treatment of moderate to" -- yes, move that. No. Determined -- okay. Take --

ACTING CHAIRMAN STERN: Elizabeth, can I suggest that much of this will come out in Question 4 --

DR. ABEL: Okay, all right.

ACTING CHAIRMAN STERN: -- in terms of filling in the boxes about the --

DR. ABEL: I need to be at the --

ACTING CHAIRMAN STERN: Or if you'd like to go there.

DR. ABEL: No, that's okay.

ACTING CHAIRMAN STERN: Can I move the question? And I guess the other important thing is not only do we have the statement, but it's adults and

children separately and the two concentrations separately.

But this, again, is only -- in a certain sense, it is a bit irrelevant to children at the .1 percent because we've said that we are at this point -- we're not sure about an efficacy superiority. So I'm wondering to make things easier can we at least take out .1 percent there since it's really not in play at the current time? And maybe we can vote more quickly so we can --

(Pause in proceedings.)

DR. ABEL: It's very confusing. It's very confusing.

ACTING CHAIRMAN STERN: But as I say, we will be defining it in Question 4 really. Dr. Epps, would you like to move the question?

MR. LIM: I move to -- I think for the interest of moving things along, I would move to Question No. 4 and address Question No. 4, and part of this question will be addressed, I'm sure.

ACTING CHAIRMAN STERN: Is that okay with everyone?

All those who believe that this statement reasonably reflects their feelings at the end of today or at the time today, so signify.

(Show of hands.)

ACTING CHAIRMAN STERN: It does reasonably reflect? Henry?

DR. ABEL: You put the "long term" back in. "Long term intermittent" --

ACTING CHAIRMAN STERN: I didn't say perfect. I said reasonably.

DR. ABEL: Reasonably, yes. I will go with that.

ACTING CHAIRMAN STERN: You don't agree. Okay. So it's five to one.

Well, now that we've done the easy things, why don't we move on to Question 4, and I think the first thing there is we would really -- in the introductory sentence, we would clearly change it to be consistent with two and three in that whatever that awkward phrasing was rather than unrestricted chronic, we would substitute the awkward phrasing there, and we would have .03 in children and both strengths in

adults.

And I guess one other thing that I hate to raise an issue. You have children over two, and one of the things in the safety discussion that struck me a little bit was the very little bit of data in a small number of children two to five where there were higher levels of absorption, which makes sense because if you look at the ratio of surface area to kilograms or any other measure of body mass as opposed to body surface area, there's the highest ratio in those younger kids.

So I guess one thing to me about the -- it's not a matter of not thinking that it should be approved, but in terms of additional cautions about our database is perhaps breaking it -- breaking another thing at some -- the two to five a little bit differently than the five and above who were still clearly children.

And I don't know if any other people either -- I don't know how you feel about this. I mean it's difficult because, on the one hand, these are kids who really need it. On the other hand, there

is some evidence that they're more likely to have higher levels, and they are the youngest kids.

And if you look at lymphoma related to transplantation, little kids are at the highest risk.

DR. PALLER: I'm a little confused because I think there was some PK data that was presented that where there was less PK data, but in terms of what was done standardly in some of the early studies looking at the actual levels of the tacrolimus in the blood, I don't think there was a problem there. Maybe I'm --

ACTING CHAIRMAN STERN: It's difficult with all of these data, but I remember one slide where there were a very small number of patients two to five separated out from other children, and --

DR. PALLER: I thought that was in the PK data presentation.

ACTING CHAIRMAN STERN: But I think that would be -- good. You can tell me slide 273.

DR. FITZSIMMONS: Close. It's 228.

(Laughter.)

DR. FITZSIMMONS: This slide shows the pediatric group that received the intended

concentration that you've just agreed on, the .03 percent, and we've broken those 78 pediatric patients that I had shown in my primary presentation down into the two to six, seven to 15 year olds, and then compared them to the adults who received .03 percent.

What you'll see if you look at those with a nonquantifiable level less than .5, the pediatrics in two to six, 70 percent of them have a non-quantifiable level, the exact same as the adults.

It's actually the seven to 15 year olds that are the outliers who have lower absorption. So the two to six year olds have no great risk in terms of blood level exposure as compared to the adults in these data, and even if you look at the levels above one or above two, you can see they're much lower even in two to six year olds compared to the adults.

ACTING CHAIRMAN STERN: But the issue here to me was if you're worried about -- if you have any concern about the possibility of lymphoma, the data is that two to six year olds are at much higher risk at least in the transplant data than are people over 17.

So the same concentration in a younger

person is more concerning to me, and not knowing these data very well, I think even a very young person, a two to five year old toddler basically is even more concerning than a seven or ten year old in terms of innate risk at least with immunosuppression.

So you have to balance the concentrations versus the potential underlying risk.

DR. FITZSIMMONS: Right, and I think it's important that, again, these are intermittent therapies. So they don't maintain these levels for long periods.

DR. WILKIN: We have a slide we also could show. I think maybe it's the one you're referring to.

ACTING CHAIRMAN STERN: Yeah, I can't remember them all.

DR. OKUN: We have a somewhat similar type of presentation as the sponsor has just shown in that there's a breakdown here looking at maximum tacrolimus blood concentrations first in the set of patients age two to six, and then there's a set aged seven to 15.

And as you stated, Dr. Stern, there is a higher percentage of patients who have blood levels

above the lower limit of detection among the patients age two to six, whereas in the patients age seven to 15, all of them have -- all of their specimens are below the limit of quantification.

ACTING CHAIRMAN STERN: And I actually had a question for you about the slide. With 16 patients, how do you get less than six percent in any cell, and with 17 patients, how do you get three percent since 1/16 is six percent and 1/17 is also about six percent?

I had meant to ask that, but unless these are multiple determinations in these 20 and, you know, the denominator, in fact, is over the number of determinations rather than the number of patients, that's what I assumed, but it would be interesting to know. N equals 17 patients and 127 or 33 determinations or whatever.

DR. OKUN: Yeah, but there are -- yeah. I'm sorry. I'm thinking out loud. I think the N refers to the number of patients, whereas the percentages refer to the number of samples, and where there were samples collected at numerous times during

the course of the study. I think that's the explanation.

ACTING CHAIRMAN STERN: And do you happen to know how many individuals of the 16 and 17 are represented, how many different individuals ever had a level above one or above two?

It's not really important. I mean, just curious.

PARTICIPANT: There's only that explanation.

ACTING CHAIRMAN STERN: That was my question. Was it the same patient who scored on both?

DR. FITZSIMMONS: That four percent. Well, there's only one patient with one single determination that was 1.19 nanograms per mL in the two to six, .03 percent.

ACTING CHAIRMAN STERN: Okay. Thank you.

So how might we best proceed? I believe we have agreed that we would change the phraseology beginning with "which" and ending in "adult certainly." Is there anyone else who feels that these data or anything else suggest any additional caution,

given this small subset in very young children, not to mean necessarily any difference in recommendation about approval, but perhaps specifically warning people that we know even less here, and that, in fact, relative to the overall database, these people seem to have a higher frequency as might be expected of higher systemic levels?

I see Dr. Paller, who I always respect her acumen, and I see I've lost her completely.

DR. PALLER: After showing these data are you still worried about two to six per se in terms of the data shown?

ACTING CHAIRMAN STERN: If we go back to this --

DR. PALLER: Because there were more in the two to six year group shown than in the seven to 15.

ACTING CHAIRMAN STERN: Right. I'm worried about the two to sixes more than I am about the six to 17.

DR. PALLER: In general, of course, right.

ACTING CHAIRMAN STERN: In general, of

course, but these data make me worry even a little bit more because I read those data as the two to six year old having a higher frequency of detectable, and in fact, above one nanogram levels, which makes sense, given their --

DR. PALLER: Yeah. I mean, there was one patient who had one detectable level, for example.

ACTING CHAIRMAN STERN: Yeah, but you know, you can go confidence intervals around that, and it can get to be quite a large number, but it's sparse data, but it goes along with everything that you'd expect or at least that I'd expect.

DR. PALLER: I guess I'd be more uncomfortable if it weren't also in the adult, that the same thing was there.

ACTING CHAIRMAN STERN: Yeah, I'm less comforted by it's okay in adults and, therefore, it's okay in three year olds. I mean, that's -- to me they are very different risk considerations.

DR. ABEL: Can we vote on those separately, the adults versus the children?

DR. PALLER: Can I just -- I think what I

don't know and what no one knows is what it means to have a level that's one percent intermittently, and no one knows that.

ACTING CHAIRMAN STERN: I couldn't agree more. It's just the question is: is it enough> If you'll pardon my using the analogy to adverse drug reaction, are these two patients enough of a signal that you want to call people's attention to it?

It's a relatively infrequent event, but it's in a subgroup that you're particularly concerned about. So do you consider this a signal like you do an adverse report of a rare disease in a drug that gets phoned in?

I mean, to me it's a signal that it's no proof of anything. It's hard to interpret, but to me it's a real signal in a group you're particularly concerned about.

DR. WILKIN: Yeah, I think it's exactly that. It's the imperfect data sort of thing trying to make something out of if. I just remind the committee that where it says "maximum blood concentration," it doesn't really mean Cmax. It just means the largest

values found on a random sampling sort of approach.

ACTING CHAIRMAN STERN: And along that line, did the sponsor ever do a study where in people on some degree of chronic dosing you did multiple determinations over a 24-hour period of time, where you could look at the variability in someone who had detectable levels, the variability over time.

I mean, I guess one of my expectations about this, that on any given day, there's likely to be less variation in the Cmax because this is a topically applied product and probably a reservoir effect than if this were an oral product or an intravenous product, but I may be completely wrong.

Anyone have any data on that?

DR. FITZSIMMONS: Yes. Specifically in pediatric populations, we evaluated .1 percent. So, again, this is three times greater than what we're proposing for commercial.

In a pharmacokinetic study in pediatrics, where we did a full 24-hour profile on day one of therapy and then another 24-hour serial kinetic profile on day 14 of therapy, and you can see here the

data that's shown from this pediatric study, and I believe this is summarized in your briefing document.

On day one you see depending on the body surface area treated as it increases across the three treatment groups. You see the AUC of 3.2, and then in the second group, 8.9 and 10.6, and then it decreases over 14 days in the highest treatment group down to 4.7.

So similar to the previous data on the day one where we have active flare disease, you see an AUC of 10.6 which drops in half by day 14, and then the therapy was discontinued.

ACTING CHAIRMAN STERN: My question was slightly different. Because you have basically shall we call it random sampling throughout the day, the question is how much are you hitting Cmax's in your larger samples, and my question would have been if you track an individual patient over 24 hours, are there levels reasonably constant, especially after day one, you know, on day seven and beyond. Is that reasonably any given time of day or does there seem to be a lot of variability?

I don't know if you have those data.

DR. FITZSIMMONS: Well, in this study on day 14, we actually measured concentration serially across those time points.

ACTING CHAIRMAN STERN: And was it pretty flat?

DR. FITZSIMMONS: There is some elevation over the time zero point, but there's not a big spike. I don't have an actual plot of that here.

DR. OKUN: Dr. Stern, if I may make just one or two comments, this information, the slide that we have up here, actually refers to data that was collection in the 12-week study. The sponsor has also conducted other studies of shorter duration, one of which, 95009, in the pediatric patients, a maximum blood concentration of 9.58 nanograms per mL was observed.

I should mention that seen with the 0.1 percent ointment, whereas it looks like you're heading towards not necessarily advocating the use of that. So I wouldn't say necessarily that in all the PK studies up till now that we've seen labels uniformly

less than one or two nanograms per mL in the pediatric age group.

DR. WILKIN: Since they're actually the sponsor's data, in your briefing document on page 35, Figure 3, the bottom panels, it's got mean tacrolimus blood concentrations, time profiles in adult and pediatric atopic dermatitis patients. Is that helpful?

DR. FITZSIMMONS: Yeah, we actually have a slide of that maybe if it would help for people that don't have the briefing document, what Dr. Wilkin is referring to, and again, just to point out, this is the 08 kinetic study that I had discussed previously, and this is with .3 percent, but you can clearly see that the profiles are fairly flat even over the 24-hour period when you get to day eight, but you do see more of a peak in that first day.

So what you're asking, Dr. Stern, is very similar.

ACTING CHAIRMAN STERN: That's helpful. Thank you.

DR. WILKIN: Well, actually the bottom

panel had the pediatric part, and it looks like there is an area of application effect; is that not --

DR. FITZSIMMONS: There are two groups of pediatric patients. There are four in each group. You'll see a 100 square centimeter and a 50 square centimeter. On day one the 100 square centimeter does have the four hour level that averages two, and then they're flat by day eight.

Again, this is .3 percent concentration, ten times higher than what we're looking at for proposed labeling for pediatrics.

DR. LIM: But along this line, this comes back to the area that is applied. One hundred centimeters square is ten centimeters by ten centimeters. So it's a relatively small area.

DR. FITZSIMMONS: That's why we went forward and performed the previous study that I showed with 60 percent body surface area treated with .1, because we knew this was a lower body surface area.

ACTING CHAIRMAN STERN: Do I hear anyone but me who might think that the Advisory Committee might advise that some special attention be paid to

additional concerns about safety and absorption both in terms of labeling and perhaps in terms of additional studies in two to five, as opposed to all children?

I guess I'm the only one. So I don't hear it.

DR. ABEL: I agree.

ACTING CHAIRMAN STERN: Oh, okay. Anyone else?

I think not to do anything formal, but I think that's an area in terms of long term therapy of two through five, less than six, because that was the break point you did, was essentially two through five.

With that extra caution, could we perhaps go through the decision table?

I'd like to add one other parameter. One of the most difficult things for me in terms of thinking about risk-benefit of this is the area of the body that perhaps has the greatest risk advantage over corticosteroids is the face, and yet in terms of my own concerns, always colored by one's own interests that's the area of greatest risk.

And I don't know. I would like the company's opinion bout how do you all feel about face versus other sites because of the squamous cell carcinoma risk?

DR. PALLER: I would just say that I'm just as conflicted as you are about this because if there's one place I'd like to do it as a first line agent, it's on the face, and I've seen so much atrophy from the use of topical corticosteroids in that area.

But I, too, share that concern, and I think one of the things that we have talked about is about the concomitant use of sunscreens. And fortunately, I've had better experiences it sounds like than you have. I've been able for most patients to find some sunscreen that is tolerated, and that's something that we certainly stress.

I think that there have to be precautions about that. I don't think anyone has any disagreement with that. I don't think it should preclude its use on the face, but I think the precautions need to be strong, and that perhaps there needs to be some definition about sunscreen use over time as that

information arises, and sun protection, staying out of sun in peak hours, the wearing of hats, that sort of thing are all very useful.

ACTING CHAIRMAN STERN: And, Henry, any?

So I think what I'm hearing is people do not want to separate out usually sun exposed areas in terms of these recommendations, but they do have additional concerns which might be reflected both in labeling and in issues for additional studies in terms of better defining what is the risk of carcinogenesis both in adults and children with long-term use.

And I actually do believe, although I agree that the relative risks are likely, if they go up at all, are likely to go up in people of all skin types. I think given the tremendous difference in absolute risk, I think a little bit more precaution.

I'm actually most concerned about people who have substantial photo damage, a history of a prior malignancy or actinic keratoses. I mean to me the presence of actinic keratoses would not be a counter indication to therapy, but would be a strong factor to consider in risk-benefit in treating an

adult.

So I think those kind of risk parameters are, in my opinion, appropriate and should be somehow considered. So I think perhaps we should deal with the adults first, and I think really in all of the adult ones as we redefined Questions 3 and 4, the committee has pretty much said that -- can we put back up with the committee said in the --

(Laughter.)

ACTING CHAIRMAN STERN: I think when we change that to long-term intermittent therapy rather than unrestricted chronic that most of the committee seemed pretty comfortable with that, but is that correct?

I think Dr. Epps was the only one who was not comfortable with that. Is that --

DR. EPPS: Regarding safety.

ACTING CHAIRMAN STERN: Yeah. Well, and I think in first or second line we've now really changed what we mean by -- we've taken what I call an intermediate position here and defined what we think its place is, and I hope everyone still feels that

way.

And I think for adults we thought we were pretty comfortable with both .03 and .1 and might wait until we get to Question 5 about some of the things that we think would be very useful to know about when to use .1 and when to use .03, but didn't have any strong feelings, "Oh, yes. Okay for this one, not for that one."

Is that a fair summary, and is that pretty much what you want to know, or do you want to vote on each of these?

DR. LIM: I thought it was a good summary of what our previous discussion had been.

ACTING CHAIRMAN STERN: Is that okay from your perspective?

Okay, and with the exception of Dr. Epps' concerns about, additional concerns about the safety aspect of long-term intermittent in children, I think there was general agreement, and was yours more in children than in adults? Okay. So for adults it was everyone's in agreement. For children, I think the difference is that at this point we believe -- it is

my sense that we believe -- that .03 is the only strength we're recommending in children at this point, pending other safety and efficacy data as potential changes; that the definition of its place is still defined by that in terms of not using first or second line, that that the definition of period of use is still defined by that, but we have additional concerns not really that changes perhaps approval, but night affect labeling in two to five year olds, and that comes down to safety concerns that we think based on the little data available and who they are make us additionally concerned about both better defining that and in anyone making the decision having a little bit more weight on potential yet undefined risk in that subgroup compared to others, other older children with comparable disease and indications.

Is that a fair summary? You mean we get to go on to the next question?

Question 5, maybe we should just go around the table and get suggestions about specific kinds of studies that people think might be useful, and in the context of what may well be practical with an approved

drug. We all know what we'd like to have for information, but the question is what's practical.

Do you want to start, Dr. Epps? We always seem to start on this side.

DR. EPPS: Well, at this point just a brief comment in regards to the chicken pox and the varicella. For example, there were, I guess, five kids who developed infection during the trial, and it would be interesting to know whether or not they had been immunized. Say, for example, none of them had been immunized. Then it would be worth having kids entering or being -- before they go on the drug, being immunized or have had the infection or proven to be immune so that you avoid that complication.

But it would be interesting to characterize, to put on my pediatric hat, whether or not those kids had had the chicken pox or whether they had been immunized and then somehow -- suppose all of them had been immunized and then they developed the infection. I mean, I guess that would have come out, but that would be interesting to know because that may affect whom you may put on the drug.

Sometimes kids who have atopic dermatitis are behind in their immunizations because physicians don't want to give them the immunization while they're severely affected. So that may be something worth looking into, especially for the smaller ones.

DR. ABEL: Of course, we need to have long-term follow-up studies of safety profile. In regard to the herpes, I'd be interested in knowing in those patients who have a history of chronic recurrent herpes simplex if this increases their frequency of outbreaks.

In regard to the photocarcinogenesis, I'd be interested in the age distribution of the adults that were treated in the clinical trials. Were these mostly young adults, or were there adults in the older age group who already had significant actinic damage?

And if so, did we see any increased incidence of actinic keratosis or skin cancer? Apparently not, but how many patients were in the older age group who could have had actinic damage?

And also, we need to address the use in patients with concomitant medical problems, such as

the immunosuppressed patients, patients with HIV, and safety in those patients.

DR. LAWRENCE: I'd be happy to respond to that if you'd like, Dr. Abel. I don't want to interfere with the committee's deliberations, but I'm going to have to, again, do this thing where I'm going to do like Dr. Abel and talk and look.

Yeah, I'll do this. That's easier.

There were six cases of cutaneous malignancy in the course of our studies. This includes both the short-term and the long-term studies. Of those cases, we had -- I have to count -- four cases of basal cell carcinoma, all but one of whom had a prior history of basal cell carcinoma within the distant past.

We had one, two, three patients or two patients that had squamous cell carcinoma in situ, and so those are the six cases that we had in our clinical studies. So there was a preexisting condition.

There was also -- I'm sorry?

DR. ABEL: What were their ages?

DR. LAWRENCE: Oh, ages. I'm sorry. The

ages were 61, 72, 62, 72, and 59. So hopefully that's helpful.

ACTING CHAIRMAN STERN: And I assume those were all in treated sites.

ACTING CHAIRMAN STERN: That's not necessarily true, Dr. Stern.

The second question, Dr. Abel, with regard to immunodeficiency, we did not permit patients with known immunodeficiency disorders, including HIV or other immunodeficiencies, such as Wiskott-Aldrich, to enter into this program. So as of this date, we have not permitted that to be done.

The other thing and comment to Dr. Epps, at the time of the studies, Dr. Paller reminded me many of the early studies with children predate the varicella vaccine. So I would suspect many of them were not vaccinated at that point in time, but I do think your suggestion is an excellent one.

DR. LIM: I think that in addition to what Dr. Epps and Dr. Abel have mentioned is one other historical aspect that we need to look, especially in adults and also in kids, you know: what previous

treatment specifically? What previous type of UV related treatment that these patients have had and how does it relate to the risk and the development of skin cancers or photodamage in these individuals?

Many of these patients probably have had UVB in the past. Some of them probably have had PUVA in the past. I think it would be important to find out what is the relationship in those group of patients with the subsequent photocarcinogenesis if there are any increase.

DR. TANG: Yes. Since there are still 50 percent of the patients who do not know greater than 90 percent improvement by the end of the year, I think it's of interest to see -- to have more data either on both efficacy and safety beyond one year of treatment.

DR. SIMMONS-O'BRIEN: I'm interested, one, in just -- forgive me about the sunscreen/sun block issues since that's going to really be a major factor, especially for the younger children. Are there recommendations as to whether screens, broad spectrum screens in the form of lotions or gels? Was there any kind of continuity in terms of what the participants

used in the study?

Because even a broad spectrum sunscreen and a gel is very different in terms of its protective effect, you know, and specifically the aerosols as opposed to the lotions and whether or not there are also actual blocks within the broad spectrum sunscreens.

I mean, I think that that's going to be critical because people are going to look, you know, to us to advise as to really to define broad spectrum. I know today we've been defining a lot of things, but broad spectrum really needs to be defined in terms of what the vehicle is and in terms of the SPF.

So anyway, that's one of the things, I think, that's going to be very important to do, and then the other would be, again, I touched on this earlier, to make certain that the patients who do have moderate to severe atopic dermatitis have just, in fact, that; that there is evidence that they have had biopsy confirmational diagnoses, and that even when they are on the medication, when they're on the Protopic, that if they're not responding in a way that

one would hope, that again surveillance biopsies are performed.

DR. LIM: Can I respond to Eva's first comment on the sunscreen?

You're absolutely correct. I think if sunscreens are not used properly, the SPF is going to be different, but all preparation of sunscreen, if it is used properly, if it is SPF 15, it really doesn't matter whether it is spray, gel, or lotion or cream. It should give you protection of SPF 15.

So but I think it is important to tell the patient that they have to use broad spectrum sunscreen.

Your question about broad spectrum is a very good one. There is an article that is coming out in the Blue Journal, coming out from a consensus conference that's responsive by the AAD that would address specifically that issue, our recommendation, that is, the AAD's recommendation as to what a broad spectrum sunscreen is based on in vitro as well as in vivo testing.

So hopefully that would help to clarify

it. Clearly, the FDA would have to act on the recommendation to see what their definition would be.

DR. MINDEL: Even though it may be unnecessary, I'd like to know what the mother who is putting on the ointment twice a day for a year, what her blood levels are. It could very, I think, relatively easily be determined whether there is anything detectable.

And maybe the outcome of pregnancies of mothers who are applying the ointment to children.

It looks like the Japanese are going to have at least a two-year running start on the use of this drug, and this is not -- it's sort of along the same lines, but is there some way of communicating side effects and problems from their FDA to our FDA?

DR. DeLAP: There are such relationships between regulatory agencies, and I think there are getting to be more all the time. So I think we've identified that as a useful area for further development.

DR. BIGBY: I am still not convinced that we have seen the correct data to make a decision about

the superiority and efficacy of .1 versus .03 percent cream, and I do think that the data are available, and I would suggest that we or that you take a look at the rate difference between those two concentrations in individual adult studies, and that it be done both in terms of patients with moderate and severe disease, as well as the breakdown in terms of different degrees of body surface area involvement.

And then I think you need to know the details of how the two adult studies are combined.

ACTING CHAIRMAN STERN: I had a few issues that I think might profit from further elucidation. One is in addition to the incidence of acute viral illness, I'd be interested in some further microbiologic studies, especially with the higher incidence folliculitises, really knowing more about the resistance and what is happening in terms -- especially resistance among Staph. and what's happening with folliculitis. Are these really infectious folliculitis or is this just because you're putting on an ointment? But why the differential between the placebo ointment and the drug?

So I'd like some further comfort about what's happening to Staph. bacteria on these individuals over time and the potential emergence of resistance.

To me the big two -- I think a very interesting efficacy issue is this whole issue of what are the differences between a short-term .1 percent followed by lower concentrations versus lower concentrations all the time, versus long term in terms of really which works the best, which I think are, you know, additional studies that would help further guide clinicians in how to optimally use the agent.

In terms of safety, I have the same two concerns as when we came in, which are lymphoma, especially in children, and I might suggest that it may be possible to do a fairly easy kind of registry, especially if you can link to SEER data so that you don't really have to formally follow people, but you can enrol people and see if the incidence in this group is any different than in any other groups, and that doesn't have to be a $1 billion study.

For non-melanoma skin cancer, I actually

think because there are no data comparable to SEER and there aren't the same kind of registries available, I think where I would look is in a relatively high risk population that is adults. Within my lifetime you won't get an answer about risk in children, and look at and see what the risk is, especially in people who use it in different areas. A reasonably complicated study, but actually if you pick your study population reasonably well, looking at higher risk individuals, it shouldn't have to be a huge study. You can power it pretty easily.

And those were the sort of further areas that I think would be useful as this drug comes into the marketplace.

Any other issues? Any other things you'd like to address to us, Dr. Wilkin?

DR. WILKIN: When I look over the question, I think you have responded not only to the things we asked, but also you've added a lot more to it. We really appreciate the in depth discussion.

ACTING CHAIRMAN STERN: Do I hear a motion for adjournment then?

DR. LIM: So moved.

ACTING CHAIRMAN STERN: All those in favor?

Thank you all very much for your patience.

(Whereupon, at 4:50 p.m., the Advisory Committee meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of:

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEETING

OPEN SESSION

Before: FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

Date: NOVEMBER 16, 2000

Place: ROCKVILLE, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis