significantly impacts the lives of patients who deal with it as a lifelong health condition.

We're asking for full discussion of the fact that this is a new molecular entity, first-in-class, for use in psoriasis patients with no marketing history in any other indication. And with those benefits and risks that you've heard, that's the discussion that we would like to have from you, and we appreciate your comments as we move through the day.

And about the trials, we have no specific plan in mind for a pre-market randomized control trial. That was a delineation of the available options and what some of them might be, so we really do look forward to your discussion. I think we're all grappling with some really significant issues for patient safety and also for patient access.

DR. BIGBY: Dr. Shwayder?

DR. SHWAYDER: I have two questions

for the FDA. Not being a statistician, how long a follow-up do you need to assure us of the malignancy risk? In other words, what time period makes you feel comfortable based on past drugs and past post-marketing cancers in years or patient years? I mean, you get 20 years when we get 20 years, but Centocor wants to do this in 20 minutes.

DR. AVIGAN: Again, I will try to just answer this in a more conceptual way. I think the important concept is that different malignancies actually have different biological behaviors, so it's hard to give a sort of one size shoe fits all answer, and that's why when you lump all malignancies together as one thing, you're actually mixing together different biological behaviors.

Another important point is that different patient groups, different indications of use, different demographic groups, may have important differences in susceptibility to certain types of

malignancies. And we learned that lesson, I think, in the case of the pediatric Crohn's patient population, which I mentioned, where it seems to be -- with all the cases that have been reported so far, that heavy skewing towards that group of that rare malignancy.

So the answer, in a way, is that we don't have a perfect method where we can at some exact time point cap risk across all malignancies, and we have to, therefore, use our judicious sense about what is acceptable in the arena of uncertainty, and bring that into the calculation of when we say for a certain indication, with the uncertainty that we're dealing with, we move forward with some -- we move forward and we approve and we indicate the drug for that use.

And so I think in the end, what we are trying to do today is just basically frame the level of uncertainty that we're dealing with -- I think, number one -- pose to the committee the difficulties of

precisely measuring risk, and asking from the committee their sense of how to deal with the large benefit/risk question, taking into account this uncertainty.

DR. SHWAYDER: I wouldn't shy away from registries. Any practicing dermatologist has had to struggle with I Pledge for Accutane, which is a complete pain in the neck and probably twice as bad as giving someone thalidomide, yet we all managed to muddle through it. And if a registry is what will help us answer the question, then I would certainly leave it on the table.

DR. BIGBY: I have two questions, and I promise the rest of the panel that I am not jumping the queue. My first question is for Dr. Ahmad. You mentioned that this biologic is being brought to the table with a much smaller size in duration compared to the other biologics. Could you give us a sense of how long follow-up, and how large were the studies of the other biologics when they came

for approval for treatment for psoriasis?

DR. AHMAD: That's a good question. I think personally, I'm not aware of the details of the other biologics of when they were approved. But I am aware that unlike other biologics, this biologic is being considered for approval for psoriasis with no prior marketing history. And I think that itself leads me and some of us to believe that there may be a need to conduct additional studies, long-term clinical trials -- in perhaps other disease categories -- before it's approved.

DR. WALKER: I think we can put up slide 33 from the backup slides from Dr. Carr.

DR. BIGBY: To save time while you're finding that slide, I have a question for Dr. Walker. Is there such a thing as a provisional approval based on delivery of a promised post-marketing surveillance study?

DR. WALKER: No.

DR. BIGBY: Again. Until that slide comes up, Dr. Heckbert --

DR. HECKBERT: This is the slide I was going to ask about, the one they're trying to get up, slide 33 in Dr. Carr's presentation. My question was, you had a column there showing assessment of long-term safety for some of the other biologic agents that are approved for psoriasis, and my question was is that -- yeah, the right-most column --

DR. CARR: Yes.

DR. HECKBERT: Is that at the time of approval for psoriasis or is that now?

DR. CARR: No, that's at the time of approval. That's what the applicant's committed to do.

DR. HECKBERT: Oh, that's what they committed to do? That's not the information we had at the time it was approved for psoriasis. And that's what we still don't have.

DR. CARR: The last column reflects what the applicant's committed to do at the time of approval, of the product for approval for psoriasis. The first two products, alefacept

and efalizumab, received initial approval for the indication of psoriasis. Etanercept, infliximab and adalimumab all had previous approvals for other indications prior to their approval for psoriasis. And the last column reflects what the applicants committed to do with their approval for psoriasis.

DR. HECKBERT: So those are commitments, but they're not what we have right now in hand? We don't have data on them.

DR. CARR: All of the studies, I would say, are underway.

DR. HECKBERT: Right, but we don't have the data on that number of people for that duration of follow-up.

DR. WALKER: That's correct.

DR. HECKBERT: Maybe each or any of those.

DR. WALKER: We don't have that amount of data at this time.

DR. KATZ: How many patients do we have from the 5,000?

DR. JONES: Can I make a revision to Dr. Ahmad's comment that of all the biologics approved for psoriasis, the first two, Amevive and Raptiva, were the first indication, and based on the SBA, as you know, the Amevive had only 756 patients with two courses of treatment, and for Raptiva, it only had 218 patients treated for one year. And recall Dr. Yeilding had mentioned also in FDA's briefing document, we had 1,285 patients treated for one year.

DR. BIGBY: No, no. But I think the issue was safety. Those drugs had large populations of other indications, but --

DR. JONES: No, no. Right. That's the point. The first two biologics approved for psoriasis had no other indication, that is NME (?) for the first indication for psoriasis.

MR. LEVIN: Did they have prior experience in other countries, though? Prior approval here?

DR. JONES: No. Amevive is still not approved anywhere.

MR. LEVIN: Okay.

DR. BIGBY: Was the other point that was relevant to this slide answered? No?

DR. STERN: No. I think the other point is what's the numerator over each of these for follow-up -- for enrollment and for follow-up for at least one year, given that these approval dates are fairly ancient? So that's, I think -- isn't that sort of your question, Bob?

DR. KATZ: Yes, 5,000 promised five years ago --

DR. STERN: Right. So what's the numerator?

DR. KATZ: How much follow-up do we have on that? According to the previous comments, we've only gotten follow-up on several hundred. Am I correct?

DR. WALKER: Right. It's less than the numbers that are listed as the initial requirement. That's correct.

DR. KATZ: But how many have we gotten since then?

MR. LEVIN: I don't think you have any patients that were treated with those drugs, because they don't work that well. That's why you don't have the database.

DR. KATZ: But some have.

MR. LEVIN: But not 5,000. Or maybe. I don't know.

DR. AVIGAN: Can I just make another point? And this is perhaps repeating. These are all voluntary programs, so none of these have this sort of TFAT (?) let's say a drug like Tysabri has, for the PML, which is a mandatory registry where we have -- we can cap risk because when we saw this extraordinary signal, we were looking for one thing. That was the example of the registry, looking for one thing and it was designed specifically where everybody who gets the drug with that particular indication will be enrolled and followed.

These are voluntary. And the

problem in a large picture sense has been the implementation. The implementation has been difficult, and perhaps the sponsor, since they've also been involved at least in one of those registries with infliximab, can share with us their experience about where those roadblocks are. This concept of assessment of long-term safety with these kinds of registries was really, as Dr. Siegel mentioned, to gain some experience looking for signals that perhaps we already had some sense of rather than sort of for brand-new things.

Let's hear what perhaps the sponsor might say about that.

DR. BIGBY: We'll hear from them in the discussion part.

Dr. Crawford?

DR. CRAWFORD: Thank you. My question's a bit of follow-up based on what Dr. Ahmad and Dr. Avigan have stated, and others in a different way. When we're looking at the

post-marketing options, some of the options, in assessing safety -- I think as a committee, we should at least kind of consider what's most optimal in terms of potential off-label uses. And when I say off-label uses, that would mean by indication, by dosage, and/or population such as pediatric populations.

DR. AVIGAN: I think that's a rhetorical question. In the sense that once a drug is approved, unless there's some very stern management program, typically physicians have the prerogative using these off-label, and using them in different ways creatively with different patients -- and so that over time, what could happen, unless there was some major concern that was articulated, there would be a creep of the way it was used and in which patient populations.

DR. CRAWFORD: Actually, it's not rhetorical. I guess I didn't ask it clearly. In terms of your experience with other post-marketing commitments, what has been most

optimal or least optimal?

DR. AHMAD: Is your question related to how much off-label use of these products can happen?

DR. CRAWFORD: No, it's related to how could we detect safety issues when the product was used off-label.

DR. IYASU: Let me just answer. This is Solomon.

DR. STRAHLMAN: Perhaps a way to answer that question is could the FDA comment on how well the Adverse Event Reporting System works, which would be of course oblivious to indication?

DR. AVIGAN: Yes, the Adverse Event Reports which we get are spontaneous reports. The quality of those reports is variable. Sometimes they will tell us why the patient was treated and give us details, clinical details, which would be very useful in assessment -- looking for signals perhaps across susceptibility characteristics, or clinical

scenarios or root causes or attribution. And sometimes, in the case, for example, of the pediatric Crohn's, that was an example of where we got some sense of patients getting an event even before it had been approved for that. So it happens, but it doesn't happen systematically.

DR. STRAHLMAN: I actually had a couple of other clarifying questions for FDA.

DR. BIGBY: I think you've kind of jumped the queue here.

DR. STRAHLMAN: I actually just had clarifying questions on the presentations.

DR. BIGBY: I know, but I think Dr. Drake is right before you.

DR. DRAKE: I have a question for Dr. Walker. And first, I want to tell the whole group from the FDA, it almost sounds like our questions are being too provocative, and that's certainly not my intent. I think you've done a very good job. I think the questions are equally applicable to the sponsors, because when

I was acting chair of that meeting -- I think it was the one in 2003 -- we had lots of promises from the sponsor, and that was a concern of the committee, that these questions be addressed. And I think the questions center around why isn't this happening. It's not anybody's fault, necessarily, it's more what can we do to make it happen.

So I hope that explains, but I guess, Dr. Walker, I wanted to ask you a specific question.

You have this risk-benefit group at the FDA. Have they looked at this? Have they been involved in this? I haven't seen any speakers from it, and I just wondered what your thoughts were on that.

DR. WALKER: This is a good opportunity for me to -- I believe you're probably referring to the Office of Surveillance and Epidemiology, which is -- first of all, I believe FDA, the entirety of the FDA, is a risk-benefit group, but specifically we have the

Office of Surveillance and Epidemiology who are a parallel office to the Office of New Drugs, and we have representatives from that group at the table. So is that the group you're --

DR. DRAKE: I apologize if I've missed hearing from them, but I guess my question is, how involved have they been in this, and are they --

DR. WALKER: Oh, extremely involved. Yes, I mean, between the Office of Surveillance and Epidemiology and the Office of New Drugs, both within FDA, I think we have a very good working relationship, and there's been and always will be involvement between these two groups in all of our applications.

DR. BIGBY: Just trying to keep on schedule. We're going to go to 12:15 and then break for lunch. The order that I have people -- and you can ask questions of anyone from this point -- are Dr. Strahlman, Dr. Ringel, Dr. Shwayder, Dr. Levin, and if there's time, Dr. Majumder.

DR. DRAKE: Mr. Chairman, point of clarification? Will there be an opportunity for us to ask questions of the sponsor later?

DR. BIGBY: Yes.

DR. DRAKE: Thank you.

DR. BIGBY: Dr. Strahlman?

DR. STRAHLMAN: Thank you. I just had one question for Dr. Ahmad. The sponsor presented in their presentation additional possible commitments for their post-marketing program which we hadn't seen prior to today, at least I hadn't seen them. Does the FDA have a view on -- because in your presentation, you mentioned that the conclusion that PSOLAR would be inadequate to address some of these issues, does the FDA have a view on these additional commitments?

DR. AHMAD: Good question, Dr. Strahlman. The fact of the matter is, we were never provided this additional information by the sponsor. We came to know actually -- we saw the slides only this morning. Thank you.

DR. STRAHLMAN: And my second question was, because this has come up several times as a point of clarification, and I don't know who would have this information, but is there some information that the committee could consider for the other biologics that are either approved for psoriasis or that are used for psoriasis in terms of what was available at approval, and despite the numbers on the right-hand column, what we actually know today? Is that information at least available for us to look at? Because one of the things you have asked us to do is make some comments.

Does anyone have that information at hand?

DR. WALKER: Can you clarify again what information you're asking about?

DR. STRAHLMAN: I guess what I'm thinking is that -- there were several questions about what we knew at the time a product was approved versus what was generally known about the product if it was approved elsewhere, and

then the last question that people asked was, based on the right-hand column there, that's a commitment, but what do we really know?

DR. WALKER: Right. Well, I can give you some numbers to match those columns. And basically, it's under half for most of the studies that were -- for which a commitment was made in terms of information that we have.

Obviously, that information is reviewed as it comes in in annual reports, et cetera, et cetera, and if there was information that arose from that that was of significance such that labeling should be changed, et cetera, that is usually the step the agency would take. So to date, we don't have information that would impact labeling, but obviously, we've heard about the utility of some of these studies.

Is that a useful answer?

DR. STRAHLMAN: It gives a context, I think, for the right-hand column. And just the last question is, is there information about how

many patients were exposed to other medications before approval was given that have been approved for psoriasis, in the other systemic therapies?

DR. WALKER: Right. Those would have been in the original applications. I don't have that data at my fingertips, but I bet the sponsor does.

DR. STRAHLMAN: So the question, I guess -- I'm sure they do. So my question to the chair --

DR. WALKER: I think we just heard some of it a few minutes ago.

DR. STRAHLMAN: No, but I think perhaps when we get -- just a suggestion would be if that information is available, we could look at it, it would help.

DR. BIGBY: Dr. Ringel?

DR. RINGEL: Yes, these are questions about the PSOLAR program. There are many reasons why enrollment in these programs may be low. Some of them have to do with patients,

some of them with physicians who may not be willing to participate. There's all kinds of reasons, but since PSOLAR has been available and since it's begun for infliximab, does the sponsor have any idea what percentage of patients to whom that program was offered have actually enrolled?

DR. BIGBY: Yeah, yeah.

DR. AHMAD: As the sponsor is coming, I wanted to make a clarification. We did receive the slides with the additional post-marketing activities that the sponsor plans to undertake, but we never received any details.

Thank you.

DR. KEENAN: So with regard to the questions on PSOLAR, just to be clear with regard to the time of initiation. There was a negotiation with the FDA, and the time when PSOLAR was agreed upon to be launched was July 2007, and it has currently been running for 11 months.

And with regard to the total number

of sites that will be offered, we intend to offer it to 450 sites around the world. The vast majority will be in the United States. Sites that are interested are ones that have been interested in finding out about the epidemiology of psoriasis. I don't have the number of sites that have turned us down with regard to their interest in PSOLAR, but I can provide that for you.

DR. RINGEL: Mostly, I'm interested in the sites that have agreed to participate and are participating. What percentage of patients agree to participate of those subgroups?

MR. KEENAN: We are allowed to track information for patients who provide consent. This is an endeavor for which individuals need to provide consent. When individuals are offered and they turn that down, that's not something that we're able to track.

DR. RINGEL: So we really have no idea what the bias in these studies is in that case, because we don't know the denominator again.

The second question is that as a backwater country doc, when I heard that this program is going to be offered at -- did I get it right, academic community centers? Is that what you said?

MR. KEENAN: There are two types of centers -- and the way that we look at it, we wanted to make sure this was -- to your point, able to enroll patients with a variety of different disease severity, both sites that are academic in orientation, usually university-based sites, as well as community-based sites would be invited to participate.

DR. RINGEL: I'm sorry, what's a community-based site?

MR. KEENAN: One that's not affiliated with a university.

DR. RINGEL: Is that a private doctor in Waterville, Maine?

MR. KEENAN: It could be.

DR. RINGEL: Thank you.

MR. KEENAN: I went to Colby College in Waterville, Maine, so --

DR. BIGBY: Dr. Shwayder.

DR. SHWAYDER: I have several questions based on the weight which fascinates me. The preamble being, as a pediatrician, I do all my bases on mg/kg, so it's like the back of my hand, you do it every day for every drug. I don't know why they're shying away from doing things based on weight. So my first thought was, did they do any sort of total weight versus BMI on their patients? In other words, were they muscular people or were they just fat?

So that's my first question. Does Centocor have any answers on that?

DR. GUZZO: We're definitely not shying away from the weight issue. It would have been easier to just pick one dose, so we actually I think are in agreement with FDA that we need to look at that. What I can show you is we have looked at BMI. Can I have the slide up, please? And we've also looked as weight, as

we've showed you.

When we look at BMI, we do see, again, in the lower weight group, in the 45mg dose, that as you increase BMI, you get somewhat lessening. But when you look at the weight versus BMI and you look at who contributes under BMI, it is actually the weight or size of the person that makes the biggest difference.

So if you're a very short, obese person, the 45mg dose may be fine with you. You could be, however, a very tall 6'2" person and larger in size and not be overweight, and then need the higher dose. So weight in our analysis is the major determinant.

DR. SHWAYDER: And I have follow-up question. Did anyone look at fatty livers? You partially answered this before about metabolism of a protein, because fat people tend to have fatty livers. Did that make any difference or did anybody even look at it?

DR. GUZZO: To my knowledge, we did not evaluate people with fatty livers.

DR. SHWAYDER: And are fat psoriatics mainly in the U.S.?

DR. GUZZO: Obesity is a common comorbidity with psoriasis. Our studies were conducted in the U.S., Canada, and Europe. In both the U.S. and Canada, there's significant obesity. In Europe, it's somewhat smaller, but you know, it's not unknown.

DR. SHWAYDER: And partly I ask this because I just came back from South Korea and after ten days there I didn't see a single person over 50 kilos. So if you're suddenly giving 90mgs to South Koreans, it might be like twice too much drug.

The other question I have, did you inadvertently or advertently give it to anyone who had viral hepatitis, and what happened?

DR. GUZZO: I'll have Dr. Yeilding address that. And for your question about South

Korea, we are only studying the 45mg dose. We did take note of their mean weight.

DR. YEILDING: Regarding your question about the advertent administration of ustekinumab to patients with hepatitis, we did not administer the drug to patients with known hepatitis B or C, so one of the eligibility criteria was that patients with known hepatitis B or C were excluded from the trial. We did not screen patients for hepatitis B or C, so we don't know whether there was any background hepatitis.

We did have one subject who contracted hepatitis B over the course of the study. In that subject, we discontinued treatment until the active hepatitis resolved, and then that patient resumed therapy and has had no other issues.

DR. SHWAYDER: One more question, Michael. Were the injections given sub-cu or IM?

DR. YEILDING: They were administered

subcutaneously.

DR. SHWAYDER: So that wouldn't make a difference in terms of body mass index, because almost everyone, you'd get it in the fat at that point, I presume. Okay. Thank you.

DR. BIGBY: Dr. Levin?

DR. LEVIN: So I'm concerned that we're sort of sitting here again with uncertainty -- being asked to make decisions in uncertainty. And perhaps relying on this magic bullet called a Phase 4 post-market study and then finding out that we have some commitments where people are trying to fulfill them in good faith but having difficulty in enrolling -- and if I understood you, Mark, that maybe the magic bullet -- maybe not -- is mandated versus voluntary; that we have evidence that getting more people enrolled occurs when it's a mandate, of course, than perhaps voluntary, but could you sort of drill down a little more.

Are we learning anything more from the studies that have reached the 4,000 or

5,000 or whatever the committed number of enrollees are than we are from the ones that haven't reached that arbitrary number yet?

So that's one question. Second question is post-FDA (?) and post, I think, a commitment of several hundred million dollars to the agency, I think we have from congress to do some of the things that are needed, can we look forward to an AERS program that's going to be more robust and sort of not 1 to 10 percent, but maybe a higher percentage of reports and the opportunity to learn much more from AERS and MedWatch?

DR. AVIGAN: Again, I think that's an open question. I think that we clearly need to improve our monitoring for safety and surveillance, and improve the tools that we use and respect their limitations.

I think part of the problem here is the toolkit that we have -- and part of the problem is that there's a built-in lag effect of having to have a sufficient exposure

population to see what the effect is, which is intrinsic to what the problem is, and that wouldn't be solved by whatever tools you had or improved upon.

So let me speak to the second point, because I think that's where what we're dealing with today -- is where we see an animal signal, we see a biological plausibility, we have a limited exposure in the human population where we don't see much, and we have a proposed indication for a skin disease.

And so I think the large question here is -- you know, do we want a larger human exposure before we pass judgment on benefit/risk with regards to this particular indication? I think that's what the question is.

Now, where can we learn that information from? It could be really an assortment of data sources, including clinical trials, uses for other indications,

developing a larger safety database across clinical trials, as well as if the drug were to be marketed, that we could then be proactive in following up on spontaneous reports and observational studies perhaps.

So what I would envisage is that we would use more than one tool in risk assessment for malignancy. The question today is the question of approval for the first indication. So I think that with what you know today, and then how much uncertainty would you tolerate.

And then the second question, then, would be how would we learn, with a larger exposure over time, really where those risks are from empirical observation.

DR. BIGBY: We're going to break now, but before we do, I just think it would be very helpful if somebody addresses the data requests of Dr. Strahlman, so just before we break and I read this statement that I have to read before we break, would

you just restate what it was you were asking for?

DR. STRAHLMAN: What I was asking for is if there is information about the number of subjects that were treated at the time other systemic -- which would include biologic therapies -- were approved for psoriasis, for that specific indication. And then for the products that had other indications or had been marketed elsewhere, what history was available.

And then finally, and although I think Dr. Walker has already addressed it, based on the commitments that had already been outlined in terms of the observational studies, what we actually knew today if we knew that information or at least had a general idea.

And again, to restate, the reason for the question is that the committee has been asked to -- the FDA has asked for some advice on how to frame that context, and since there seem to -- I wasn't clear on what

had been done for which drug. I thought it would be helpful.

DR. BIGBY: We'll now break for lunch. We will reconvene in this room in one hour, so that's at 1:15. Please take any personal belongings you want with you at this time. The ballroom will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Panel members, please remember there should be no discussion of the meeting during lunch among yourselves or with any members of the audience.

Thank you.

(Whereupon, at approximately 12:15 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:13 p.m.)

MS. WAPLES: Everyone, please take your seats, we're about to begin.

DR. BIGBY: We're going to start the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial

information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourage you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with

dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation. I will also add that each of the speakers is limited to an eight-minute presentation.

MS. WAPLES: We have first coming up the OPH Speaker No. 2.

DR. DOUGHERTY: Hi. My name is Bernadette Dougherty and I have no financial affiliation with Centocor. However, my doctor has paid for my trip to come out today.

I am a psoriasis sufferer and I was self-diagnosed at about the age of 24. Now I say that I'm self-diagnosed because I have a family history of the disease, and my mother, brother, aunts have it. I had a small plaque behind my knee for over a year, and at the time, my father was undergoing a battle with cancer and the stress from that is what finally made my psoriasis just explode. And I have it on every part of my body.

Over the years, I've used different types of treatments for this disease: creams, ointments, shampoos and soaps, pills, UV lighting, natural sunlight, tanning bed, lotions. I currently use a biologic and I did participate in the clinical study. I was in a Phase 2 study.

What my routine would always be is if I had something special coming up and wanted my skin to look good, I would go ahead and apply all the topical ointments, creams, foam in my hair, all over my body. I would do that at night and just pray nobody would come to see me.

The doctors always recommend you to do this twice a day. There's no way you can do that and get dressed and go to work. It didn't work for me, and I don't know any other sufferers that it works for.

I currently am on a biologic that I self-inject every two weeks and actually I'm having some flare-ups right now, so I am

using ointments on top of my biologic.

Now, there are some negative impacts. The main one I think is the mental and emotional toll. I'm not going to die from it. My father had cancer, but you know what, it's just as debilitating. It is a disease. It's not a skin disease. It's a disease like everyone else has. It's this vicious circle. You waste your time, your treatment -- there's no cure for it.

It's the continuous questions from people who don't know, people that should know what the disease is and they don't. Is it contagious? How did you get it? I've had people in hospitals ask me that that should know -- old, young, blue collar, white collar. Nobody knows, because it's considered as not a big disease. Well, it is a disease if you have it.

There is some positive impacts. I guess you have to get a little creative, so I'm never alone. I speak of it as if it's a

second person with me. They're not happy today. They're a little better. I've had it for over 20 years, and so I have to take it for me. I just have to accept it because right now, there's no treatment, so I have to live with the best that's out there right now.

My involvement with IL-12 actually came when I was at one of the low points in my life with psoriasis. There were different times I would go into work with just handfuls of ointments and stuff, and I would just cry. And a friend actually heard an advertisement on the radio where a local doctor was looking for patients to participate in the IL-12 clinical study. So I went in and visited Dr. Leonardi and his staff, and it was determined that I was a definite candidate for the study.

So I had my first dose in December of 2003, and the results -- actually, if you'll switch ahead one more so they can see

these pictures. This is my results. The one on the left, is what I looked like before I went in and had anything. I have all the little small ones, so the ointment and stuff to try to dab on each little one, there's no way it can happen. My entire body looked like that. That's just kind of like the little hip area. And what happened was I had one injection for four weeks in a row, and then I had one at week 12 and week 16.

Now, what we found out afterwards is I only had one injection, and that was my very first injection. And that's what I looked like at week 12 still. And I believe my skin was still pretty good for a couple of weeks, maybe a month after that. It's just unbelievable.

You know, I mean, I was running around the office and my family saying, look at my skin, check this out, and everything.

So it was just a huge improvement for me. Now, I guess I'd have to say along

with this, there is kind of one major side effect -- and I'm being a little facetious here, but it cuts down on my free time, because now I'm not at home putting on all these different ointments and everything, I'm out doing things. I'm out spending more money because I'm happy again and stuff, so that's kind of some of that.

Now the positive impact is my beautiful skin. And it's given me the courage. I don't know if I mentioned, I am from a small community in southern Illinois, a little farming rural community. There is no way I would be in front of the FDA talking to you guys if I looked like I did before. So I mean, it's given me the opportunity to enjoy my life again, and for some people just to give them their life -- I mean, I visited with the Centocor's manufacturing plant in St. Louis a few years back, and I told their workers, they're probably saving lives.

If they're not saving lives, they

are definitely saving souls and spirits, because they've done that for me definitely, which is all part of why I'm here today.

This drug definitely needs to be passed. Other people who weren't involved in the clinical study need to have this chance to get this medicine. I know you guys are talking about maybe injecting once every 12 weeks. That's unheard of with a psoriasis sufferer. If we could inject once every three months and go on, we'd be almost like human people. We wouldn't have to get all the questions as to what is that, is it contagious.

Again, it's not cancer, we're not going to die. So you know what, it gets pushed under the rug.

And then that's part of the vicious circle, too, because you feel bad that people aren't paying attention to you, but yet people are out there with serious disease. But you know what, it has the same toll on

us. I mean, I've read where suicide rates are higher with psoriasis patients, and it's all the mental thing, and it's all trying to explain to people what is going on.

So I told the Centocor people a few years ago that they were definitely my heroes, and I still believe it. I can't really talk enough about this. It's just wonderful, and I thank you very much for this opportunity. And I would just ask that you please vote for it, because it's my miracle drug and it can save people's lives.

Thank you.

DR. BIGBY: Thank you.

MS. WAPLES: Number 3.

MR. FARRINGTON: Good afternoon. My name is Dan Farrington. I'm a member of the National Psoriasis Foundation's Volunteer Board of Trustees. Every year, the Foundation receives financial support from thousands of individuals and approximately a dozen pharmaceutical companies that provide

unrestricted funding. Our corporate sponsors include Centocor as well as its competitors.

I'm pleased to be here today on behalf of the National Psoriasis Foundation and the community of millions the Foundation represents to testify in support of ustekinumab for the treatment of moderate to severe psoriasis. Although I am personally fortunate to have only a mild case of psoriasis, I'm involved in the psoriasis community for those less fortunate than I who are stricken with the extraordinary and debilitating burden that this disease can create.

I'm also here for my children, who likely have a genetic predisposition to the disease, as it runs in my wife's family as well as mine. It is critical that both today's patients as well as tomorrow's have available to them a wide range of treatment options.

As many as 7-1/2 million Americans

have psoriasis, and approximately 1-1/2 million of them have moderate to severe disease. These members of our community live in frequent physical pain and can have trouble with the normal daily activities that most of us take for granted like going to work, lifting our children, playing in the park, or even just walking.

When thick, burning, cracking, and bleeding psoriasis plaques cover significant portions of one's body, even the smallest action can be painful. In addition to the obvious complications of the disease, recent studies have established that those of us with psoriasis are at increased risk for other serious diseases, including heart disease and diabetes.

In addition, up to 30 percent of psoriasis patients develop psoriatic arthritis, a painful arthritic condition that can impair functioning, disable and deform. The mental burden of the disease is such that

suicidal ideation is higher for those of us with psoriasis.

While the number of available treatments for psoriasis has grown over recent years, there is still a significant need for additional effective treatments. Psoriasis presents uniquely in every individual, and treatments that help one person may not help the next. In fact, an individual's psoriasis typically changes over time in severity, location on the body, and how it responds to treatment.

Psoriasis can be relentless and unpredictable. Through the work of the National Psoriasis Foundation, we hear of people in desperation who will try virtually any option that brings with it a ray of hope -- for example, drugs that are banned in the United States and therapies that have no proven efficacy.

Many patients are anxious to participate in clinical trials -- possible

risks and likely benefits have not been established.

Many patients cycle through accepted treatment options unsuccessfully or only temporarily successfully, and ultimately are left at the end of the treatment road with no alternatives. This is particularly critical for patients taking biologics, as the current biologics on the market target only two different mechanisms of action.

Unfortunately, it is common for these biologics to work for a time and then lose effectiveness. In fact, 30 percent of respondents in our surveys experienced difficulties with currently available biologic therapies, with lack of efficacy, loss of efficacy, and side effects being the top three reasons for difficulty.

Those same surveys found that one-third of psoriasis patients are very unsatisfied with their treatment options. Because ustekinumab is based on a novel

mechanism of action, the availability of this drug for the treatment of psoriasis would create another important option for people with difficult to manage disease. In addition, compliance is likely to be good due to the long-lived efficacy and the infrequent dosing of the drug.

Pain, disability, loss of productivity, low self-esteem, fear, psoriasis brings all that and more to the lives of people affected. That's why people with psoriasis are willing to take great risk and to go to great lengths to find treatments that work.

The National Psoriasis Foundation encourages patients to consult with their physicians to weigh the benefits of all systemic treatments, including ustekinumab, with the known and unknown risks. The Foundation supports plans that would enhance the understanding of the long-term risks and potentially mitigate them.

On behalf of the National Psoriasis Foundation and the millions of people with psoriasis in the United States today, and those who have yet to but will develop the disease, we urge you to today strengthen and expand the treatment choices for psoriasis patients by supporting the approval of ustekinumab.

Thank you.

DR. BIGBY: Thank you.

MS. WAPLES: Number 4.

DR. MENTER: Dr. Bigby, members of the advisory committee, FDA members, patients, consultants and guests, my name is Alan Menter, and I am a practicing dermatologist in Dallas at Baylor University Medical Center, where I spend approximately 60 percent of my time involved in both clinical psoriasis treatment as well as research.

I'm here today in my personal capacity representing the International Psoriasis Council, an international group of

leading scientists and dermatologists worldwide with an interest in science, research, and treatment of psoriasis. We represent 17 countries internationally. I currently serve as its president.

From a conflict of interest perspective, while I have certainly participated in clinical trials that you've heard about this morning for ustekinumab, and have been a consultant for Centocor as I have been for all the other biologic companies involved in psoriasis treatment and research, I personally have paid for my own airfare here today, and I do not own any stock in any companies, including Centocor.

So why am I here today? Why have I decided to personally come today? I have two brothers with psoriasis as well, so I've lived with psoriasis all my life. I remember vividly the days of methotrexate, 1971, when we first got approval -- and I was a young resident -- and how excited we all were to

get methotrexate.

In 1979, when Dr. Stern and his colleagues at Harvard gave us PUVA treatment. And then cyclosporine in the '80s and '90s, and then finally psoriasis joined the biologic era -- late, as compared to all other diseases, all other immune mediated diseases -- which psoriasis actually has far more patients than, including multiple sclerosis, rheumatoid arthritis, Crohn's disease, et cetera.

So what is it that makes this day unique for us? I think listening to the excellent presentations this morning, and particularly the excellent presentation by Laurie Graham on the mode of action of ustekinumab, I think we have to recognize that we have now the first drug that actually has a genetic, biological basis for treatment in psoriasis specifically.

In other words, we've heard a lot about IL-12, 23, we now have a very -- a gene

that is very specific for psoriasis that is directed at IL-12 and 23, which gives us a pathogenetic mechanism for treatment.

When I was here in 2003, along with Dr. Drake and others for alefacept, we had never heard of IL-17 or Th17 cells. These are now center stage in psoriasis, and this is the drug that addresses it. Does that mean that all other drugs that we've had before -- all the five biologic drugs and the three systemic drugs, the other eight drugs, are obsolete? Absolutely not.

I certainly treat patients today in our large clinic with all the other drugs, and have approximately in our clinic 800 patients taking systemic therapy. I speak to my patients on a daily basis.

I think you've already eloquently heard from some of the patients the way they feel about the disease. Quality of life, as Dr. Kimball discussed, is a very, very important part of the process, and I think

anybody who negates the quality of life of this immune mediated systemic disease that has comorbidities on a par with the diseases I mentioned such as multiple sclerosis, rheumatoid arthritis, and Crohn's, has never seen a psoriasis patient or never lived with a psoriasis patient as we do on a daily basis.

So I've also considered the eight questions that have been posed to the advisory committee in the discussion this morning, and putting psoriasis registries into perspective, which I think is vitally important as you people make the informed decision about this drug, registries in dermatology are inherently difficult.

We've heard about the I Pledge registry, Dr. Leonardi, who's here today and myself actually are on the advisory committee for the PSOLAR Registry.

I just called our clinic at lunchtime today to find out in the six months

that we've been enrolling patients, we've heard it's taken 11 months to take PSOLAR underway, it took us about five or six months to get all the paperwork done. I think you posed a very eloquent question as to where are the numbers about these registries.

We currently have 185 patients on infliximab. We have 36 patients enrolled in PSOLAR. It is extremely difficult. There's a number of patients who do -- refuse. There's patients I've known for 25 years saying, no, I don't want to do that. And they're there for three hours in our clinic, have all the time to do it.

Raptiva Registry that you've heard about as well, which was unique. Basically, we have approximately 100 patients taking Raptiva. We have 12 patients on the Raptiva Registry. That is not enough, and we are people who have an infrastructure in a clinic totally dedicated to psoriasis where we have nurses and staff who can help us.

Practicing dermatologists unfortunately may not have the infrastructure, but yet I do believe registries are critical and important, particularly as we go through the ustekinumab.

And the other important issue relating to numbers. Psoriasis still, after 5-1/2 years of biologics, still only has 55,000 patients taking biologics, which means less than 1 percent of the total U.S. community is taking a biologic drug as we speak. And the United States accounts for 70 percent of the biologic use worldwide, so we are leading the world in biologics.

We are under siege politically in the United States, and standing here near Washington, we are under siege politically, we are under siege economically. I don't want us to be under siege scientifically.

Having traveled over the last few years -- few months, I might say, to Latin

America, to Asia, to Europe, our colleagues there look to us for leadership scientifically -- and in the psoriasis arena, I believe we have provided them with leadership over the last five years, witnessing the numbers of patients taking biologic therapy.

But yet, biologic therapy for psoriasis is still in its infancy. We are late to the game. We were early to the game with methotrexate -- 10, 15 years before rheumatologists ever used methotrexate, we had it approved for psoriasis. So please, I beg you, do not let psoriasis suffer, because we have 6 million patients out there, because we have expensive drugs -- psoriasis cannot be belittled in relationship to Crohn's, diabetes, rheumatoid arthritis, and other diseases of the immune system.

The quality of life of our patients are as adversely affected as in those patients as well.

So finally, in my last minute, I do believe that we do have effective therapy for psoriasis. A great number of patients, as we heard, are still not currently taking therapy for psoriasis, and ustekinumab does have great promise.

As Sir William Osler, the father of American medicine who spent a lot of his time here at Johns Hopkins, not too far away, said, "Listen to your patients. They will tell you." And as I proudly wear today my William Osler Society tie, I urge you to listen to patients and listen to the science, and hopefully, we can produce safe drugs that will be valuable to our patients for the long term.

Thank you.

DR. BIGBY: Thank you.

DR. PARANZINO: It's tough to follow a giant like Dr. Menter. Now I know how that guy Rocco Mediate felt yesterday putting after Tiger Woods.

My name is Mike Paranzino. I'm the president of Psoriasis Cure Now, which is a patient advocacy group that I founded in 2005 to advocate on behalf of the moderate to severe psoriasis patient population.

Psoriasis Cure Now has received unrestricted funding from Centocor as well as several of its competitors. We also receive hundreds of contributions annually from psoriasis patients and their families and friends. But I have a bigger conflict of interest which I want to disclose, and that is that for the last 20 years, I have had severe psoriasis. My brother has severe psoriasis. My mother has psoriasis. Two of my nieces who are in elementary school have psoriasis.

And I've made many friends in the last few years through Psoriasis Cure Now of people around the country. Most of them are e-mail friends who have devastating psoriasis that's negatively impacting their lives.

So the decision you folks make today and that the FDA ultimately makes is likely to directly impact my life and that of my loved ones and friends.

Psoriasis is a serious disease, and I feel that we have to go back to the basics and say that, because psoriasis has been traditionally defined through its moderate cases. And we're fortunate that two-thirds, maybe three-quarters of the cases aren't mild, but that has meant that the other proportion of us, maybe up to 2 million of us, have been sort of lost. No one would suggest that MS is mild just because the TV stars -- the guy, Montel Williams, is a huge star -- no one would define it that way.

There are people with Asperger's Syndrome running companies and having wonderfully successful lives, but no one would suggest that autism spectrum disorder is not serious. But psoriasis has not been able to convey the devastation that it can

cause -- the patient community has not been able to do that yet. We have to keep working on it.

Now, Drs. Kimball and Lebwohl made great progress towards that in their remarks earlier, but then as Dr. Thiers, if I'm pronouncing it right, highlighted, when a patient hears a non-life-threatening condition for which numerous therapies exist, I've got to tell you, it hits you the wrong way, and I wish that FDA as part of its presentation had included a segment conveying the seriousness of the disease. I'd like to hear that from my government and not just the people representing industry, so to speak, today. It would be wonderful to hear that from the FDA.

I do want to take a minute and read a couple of excerpts from e-mails -- incoming e-mails that I just culled the other night from people that have written in the last 60 days or so to Psoriasis Cure Now, because

they can't all be here -- and in two sentences, most of these people do a better job than I could do if I took the whole eight minutes.

A man wrote, "I've had psoriasis for 22 years. I'm tired and my family is suffering because of me. The only thing that has kept me from killing myself is my kids."

A woman wrote simply, "My life has been destroyed because of my psoriasis."

Another one says, "I'm 24 and fear that I will never find a girlfriend or wife because of finding my psoriasis too awful."

A man wrote, "I cry a lot. The pain that people go through is indescribable."

A woman wrote, "I'm 62 and have had psoriasis for six years. I struggle every day emotionally and mentally. At one point, I did not care if I died because I felt so nasty."

Another man writes, "I have had

psoriasis for nine years and it brings me tears whenever I see my skin. I always cry and ask God, why me? I didn't ask for fame or riches. All I want is to be normal like everyone else."

And e-mail after e-mail uses the word "normal," we find.

Another one. "I have had psoriasis for too many depressing years. I'm 43 and have had it since I was 17. It stopped me from being a Marine."

Another one. "I just want to feel normal."

Another one. "I usually do not go into public places because of this, and pretty much am a shut-in." Here's a 36-year-old woman, self-described shut-in. "I just want to feel normal."

And I'll close with one because it conveys the panic and fury of someone when they're in a psoriasis flare, and I've been there and certainly you've seen your patients

in this spot. "Psoriasis is robbing me of my life. I can't sit or use the toilet without pain. My arms, legs, and back are getting crusty and cracking. I have it on my head so much that it never, ever stops itching. It is in my ears and progressing all over. It started in the bends of my body. It has become a creeping monster consuming me and I need help."

There's more, but you get the point. And what it conveys is even with five approved biologics -- oral systemics, UV light, topicals, we still have people in 2008 in severe distress, and they need options, they need additional options.

Obviously, for whatever variety of reasons -- cost is an issue, insurance coverage is an issue, fear of the unknown, et cetera -- we're not reaching a lot of people. A couple of those e-mails came in the last week, so it's ongoing. And that is why I'm here, to urge you to support ustekinumab for

the treatment of moderate to severe psoriasis.

I think it hasn't been directly addressed. It's sort of been tangentially mentioned that approval and use in an actual clinical setting will help. It will speed probably a lot faster than a clinical trial setting. Actual patient years of actual patients with comorbidities in the real world, and if we could get the adverse event reporting system improved, that might take us a good distance toward getting the kind of answers we all want.

And believe me, I with a one-year-old, I would like to know the long-term implications of my psoriasis treatment, so I'm all for a vigorous post-approval system or systems, studies -- and again, if we need Congressional action on action event reports to strengthen it, let's hear it from this committee.

We have media in the back. We have the FDA here. Let's make it happen. We have the National Psoriasis Foundation, best in the business, we'll take it to the Hill. Let's do what we need to do to improve the system, but people are suffering today. I've met a few people 0 for 5 in biologics, which seems hard to believe. They're almost out of options. People laugh at me. I have about 30 percent BSA right now. Why am I not trying other options? I've been there when I've been out of options when I was in the hospital in 1990. I'm literally saving some in case everything falls apart.

So in closing -- by the way, as an aside, I do support -- I believe we should have a self-administration option. I watched a nine-year-old in the playground the other day do an insulin shot. I'm not even sure he put his soccer ball down. Sub-cu is not hard. I'm a needle chicken, and I can tell you it's really not a problem.

So in conclusion, if I can even find the card where I was going to conclude -- I'll conclude with this, which is whatever programs are put in place to address these efficacy and long-term safety questions and concerns, certainly this committee and the FDA and Centocor should work together and come up with a robust plan, and then Centocor has to fulfill the commitments it makes. And it's not enough to hide behind Johnson & Johnson or Centocor, these are individual commitments that some of you are going to make, and you have an individual responsibility to fulfill them for me and my brother and my nieces and all these people represented here.

So thank you very much for the time.

This debate is so exciting. I love the afternoon session. I've been to some of these before, and I'm grateful that you folks have committed your lives to helping

psoriasis patients.

DR. BIGBY: Thank you.

MS. CLEMENTS: Mr. Chairman, advisory committee, FDA, all guests and patients. I have no financial relationship with the sponsor or any pharmaceutical corporations, but the National Psoriasis Foundation did help me get here today.

My name is Ellen Clements, and I live in Rockland, Massachusetts. I'm 60 years old. Why as a woman do I admit that? Because I was only diagnosed with psoriasis and psoriatic arthritis three years ago, but I've had it my whole life.

I was misdiagnosed as a child, because back then, there was little known by the general practitioners of the day. I had it on my elbows and I had it on my legs, but my parents were told that it was eczema. And then as a teenager, I started developing some infection, like in my navel, and the doctor said stop wearing your jeans so tight.

And then as an adult, I developed severe plaque psoriasis on my head, but every doctor and even a derm at the time told me that it was just severe dandruff.

So many years passed with me trying to take care of it myself with just some over-the-counter stuff. But then everything changed. I went through a very, very stressful time at work. I was sent away for 10 weeks on the road and during that 10 weeks of increased stress in my life, I had what you'd call a very severe flare. It came out. I had severe plaque all over my head. It came out all over my arms, my legs, in my ears, around my ears, and what wasn't talked about today very much, but it does attack every orifice of your body. And I started having peeling, cracking, bleeding, painful lesions.

And at the end of that 10 weeks, I brought myself to a derm who insisted take a culture or a biopsy of one of these lesions

on my body, and it was found that all this time, I had psoriasis.

So for the first several months, we used every lotion, potion, gel, cream, dandruff shampoo, and then medicated shampoos, steroid products -- and steroids scared me -- but nothing worked. So then I went on an oral therapy and UVB treatment three times a week for a year, and that, too, had some benefit, but it didn't really work very well. So I went on my first biologic, which took several months to get approved, and then when it did, it didn't work.

So at that point in time, it was decided that I should try the next level of biologic. But at that very point in time, a clinical trial became available, and I decided that maybe that's the way I should go.

Life has been difficult in so many different ways. The constant itching, pain, flaking, excessive layers of flakes that just

covered my home, my car, my office. It was all over my clothes. Professionally, it hurt my career. I was a senior vice president of a Fortune 500 company. All of the sudden I'm not around very much, I'm always at the hospital having treatments. And little by little, I saw myself being taken out of a highly visible position and sitting at a desk in an office where I wouldn't be seen so much. I decided to leave that company and I did, and I work for a very supportive company now, but I'm doing what I did 20 years ago, so that hurt in a lot of ways.

Now, I was only diagnosed three years ago, and at that time, I came to realize that two of my son's children had psoriasis, and all that time we thought they had eczema. So they have now been diagnosed and they're getting treatment, but the kids torment them. It's so sad that I can't help them in any way. They both play sports. And so the locker room has become a very bad

source of both embarrassment and also torment.

My daughter had a baby about a year ago. That's kind of what brought me here today. The fear in her eyes the day she came to me when that baby was three months old, because skin was peeling on her head, because she thought she was going to have what her mom had all these years. The fear in her eyes. I'll never forget.

The baby had cradle cap, which is common for babies, but the fear is still there, will she get it? My family has lived with me through these years and they've seen what it's done to me.

So I had two very clear things I needed to do. I needed to help. I'm participating in a Phase 3 clinical trial right now, which seems to be helping, thankfully. I've only had two shots so far. And I participate with the National Psoriasis Foundation and come to Capitol Hill each

year, and meet with legislators in an effort to find a cure.

I don't know where this journey's going to take me, but I know what I'm doing is important not just for me, but for my children, my grandchildren, your children, your grandchildren, the children's future. I'm reminded every day of the pain, the lesions, the humiliation, being excluded as a kid from being able to play in the pool.

So this disease really has to be stopped. We need more treatment options. So I'm here today to ask you to please consider that this isn't a terminal disease, but it kills a little piece of me and everybody else every day. So please help us by considering and approving what you're here to approve today.

Thank you.

DR. BIGBY: Thank you. The open public hearing portion of this meeting is now concluded, and we will no longer take

comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

I just want to go back a little bit to pick up some questions and questioners that weren't covered this morning.

First one would be Dr. Majumder.

DR. MAJUMDER: I actually would have some questions for the presenters and the public, if that's permissible. One of you addressed the issue of self-administration, and I would just like to probe that a little further. I think the concern is not only that there might be issues with the actual injection, but that visiting the doctor's office on a regular basis -- say every 12 weeks, would be important for ensuring careful monitoring.

At the same time, it may very well be burdensome to go into a doctor's office every 12 weeks, but I wondered if you'd

expand on your perspective on that particular issue -- looking at that piece of not just, you know, can you inject, but ensuring close monitoring.

MR. PARANZINO: I think in the reality of medical practice today -- for one, doctors continue to have an incentive to get the patient in once in a while because all those phone calls I do with my doc doesn't bring him a penny of revenue, so there's a natural incentive there, since we just talked about financial conflicts.

In addition, we can thank the trial lawyers -- there's malpractice reasons as well -- most derms are not going to write a three-year prescription and say, go take your 12 shots, we'll see you in three years. So I think there's natural -- there's a natural control in not getting out of hand.

And also, the reality if you do make it four times a year and you have to go in, you fight, you set up the appointment, you go in, it's going to be a wave with your

doc, and you're going to see your nurse for a minute, get your shot, a little bit of small talk. I think we just -- we have to look at the real world of how it's likely to play out, and not just wouldn't it be nice if we all met with our doctor every 90 days.

Actually, I do meet with my doctor every 90 days, but I think that's rare.

DR. MAJUMDER: I actually had some questions carried over from the earlier discussion, if that's okay. I can address those now. One of them was for Dr. Jadhav.

I'm a layperson. I'm wondering if you could help me. The sponsor, I think it was slide 78, I don't know if you can pull it up -- but in terms of the two-step versus three-step, had presented some data that seemed to support two-step, or suggested that for the middle group, it really didn't make a difference according to their data.

And I wondered if you could comment on, if not the specific slide, just if you

recall that data suggesting that for that intermediate weight group, at least in their study, it didn't seem to make a difference to have a higher dose.

Is it possible to pull up a slide from the morning? It was 78.

DR. BIGBY: While they're finding the slide, did you have other questions?

DR. MAJUMDER: No, that's it.

DR. BIGBY: Do you have it? Rob, do you want to ask a question about the survival of the patient that has the genetic defect in p40?

DR. STERN: Yes. I was wondering if there was any data on survival in those people who are IL-12-deficient and in their relatives, and also the pattern of disease seen in them beyond the two infections that were talked about.

DR. JADHAV: Can I answer the previous question?

DR. BIGBY: Just hold on.

DR. JADHAV: No problem.

DR. ELLIOT: Thank you. I'm Michael Elliot from the Clinical Immunology Group at Centocor. There are various genetic defects that have been described in various parts of the -- shall we say interferon gamma pathway -- and the relevant defects with regard to our discussion today are the defects that occur in IL-12 p40 or in its receptor, and the specific clinical syndromes that these patients present with include disseminated BSG infection when they receive a BSG vaccine, regular mycobacterium tuberculosis, and environmental mycobacterial infections. As you're aware, we're all exposed to these environmental mycobacteria all the time through soil and water exposure.

The pattern is interesting in that these infections generally present during childhood. And from the data that I've seen, at least with regard to environmental mycobacteria, once the patient is identified

and treated, it's rare for these to recur and the patients survive very well.

There have been examples of patients who have presented with mycobacterium tuberculosis or TB or with a disseminated salmonella infection as well, and they can have a more serious outcome if they're not recognized and treated early, and there have been deaths reported amongst those patients.

But if you read the review papers, you'll see that the authors describe the phenotype in general as surprisingly limited and surprisingly mild compared with what we might have predicted from mouse studies.

Does that answer your question?

DR. STERN: Yes, thank you.

DR. JADHAV: Can I have the slide up? Okay. So let me rephrase the question. Also, let me know if I understand your question. Your question is, from the data shown by the sponsor -- which is my slide, the numbers are

similar so exactly similar slide, but it's a part of my backup slides.

So what was shown by the sponsor is less than 70kg on a 45 and 90, there's no difference, but 70 to 100 also, you don't see any difference.

However, the difference is seen in greater than 100. And your point, I think, is the data does not show any difference and the model does show a difference, so what I'm going to do is I'm going to show two database evidence why I think this particular graph could be misleading, and also I'm going to offer an explanation why model does what it does.

So what I did is -- as you know, this data came from a 12-week time point from a 45mg and a 90mg treated patients. But we also know that there is one more group, placebo patients was switched over to 45mg and 90mg, so if you consider that at week 24, which accounts to week 12 -- I included in

the data just side by side comparisons. Now what happens is the 70mg group, 50 patients per round -- in 90mg, there's an additional 150 patients, now it shows difference.

The question you should be asking is why. And let me put it in perspective of how much of a difference we are talking here, about 6 to 8 percent. Anybody who has done a mortality/morbidity study that has a small difference would know that the comparison on the left as well as right does not have enough power to detect the difference.

That's the first database evidence. And the second database evidence is -- if I can use sponsor's slide, please, slide No. 73 -- yeah, so the slide No. 73 is again PASI 75 response at week 28 for 45mg and 90mg-treated patients. If you look at now, these are divided into three subgroups, which I'm pointing at 70, 80 and 100, what you see is 45 and 90, there is a definite difference at each point.

Why did this happen?

There's another point to the power. It is not just the sample size, it's the duration of the study. So if you go later than 28 weeks, you're able to see the differences. So 90mg does offer more benefit even to 70 to 100 -- that's my conclusion -- than 45mg.

I'll get -- these are my two database evidence which I think should be considered. And I'll go back to my models that I showed you to tell why the model does what it does, because -- see, in the model, it does not really regress with respect to weight; it brings in concentrations into the picture.

And with respect to concentrations, we have seen that there is this continuous relationship, so the weight is implied, not a part of the model per se. So model operates under -- if I can use a loose term -- infinite (?) sample of

assumption -- so if you were to design the last study (?) to detect those differences, I am convinced that you will see differences in 70 to 100.

Does that answer your question?

Thank you.

DR. BIGBY: Rob.

DR. STERN: I have sort of a related question. If you look at those graphs, you wonder whether we're really dosing small people at 45mg at what is a reasonable minimal effective dose -- just as we may be overdosing in maintenance, are we perhaps overdosing part of the population and not having really established the minimum effective, and therefore the safest dose?

DR. JADHAV: I agree. After you asked the question in the first round, I thought about it. And so far, I would say we don't have a lot of data to conclude even if the lower doses would be beneficial or would maintain. There is some data, because if you look far out to

week 28, the lower concentration subgroup does do a little worse than the high concentration. So partly, there is data to suggest that you do need high concentration even later on, but I'm not sure post-week 40 or so if those differences will still play out, but we don't have data to support that.

DR. STERN: I think mine is a more general question. If you look at how we use old-fashioned systemic agents -- higher doses of methotrexate work better, but they're more toxic, and there's always a tradeoff between response, whether it's percent response or percentage response and dose, and when I look at your curves where light people had the very, very high response rates, you just wonder, are we optimally dosing with respect to risk versus benefit?

DR. JADHAV: I don't have a comment. I guess that's the exact discussion, I'm saying.

DR. BIGBY: Thank you.

DR. JADHAV: Thank you very much.

DR. BIGBY: I think that we should forge ahead here and start to address the questions.

DR. JONES: Mr. Chairman, can we --

DR. BIGBY: Yes. You mean about the -- yes. Correct. Yes, please.

DR. KRUEGER: Hi. For those of you who don't know me, I'm Jim Krueger. I'm a dermatologist. I'm a professor at Rockefeller University. And actually, my lab has been responsible for much of the information about the inflammatory basis of psoriasis, the cytokines that are involved, and the inflammatory pathways.

I am a little bit concerned about the way the discussion has gone to frame this particular antibody. And so I need to make a general comment about this, and I would ask that the slides that I brought along with me could be brought up. So if I can have the slide up.

So one of the things that we have

been trying to do in psoriasis is to identify the critical pathways --

DR. BIGBY: You were asked to address the question about the --

DR. KRUEGER: This is --

DR. BIGBY: No, no. The question was about what the other biologics -- what data was presented in terms of their numbers and length of follow-up. We're not going to have another lecture.

DR. KRUEGER: May I make 15 seconds of comment? No, you're denying me that? I will take the slide -- the last slide in this.

I was present at both of the advisory committees that met to consider alefacept and efalizumab. Both of these were new immune inhibitors that were brought into the treatment of psoriasis, and for which psoriasis had been the only major test indication in humans for these.

Alefacept was the first drug approved for psoriasis, and it is a fusion

protein that binds to CD2, and therefore has depleting effects on memory T-cells. So there are -- were some concerns about immune suppression -- in fact, it demonstrated immune suppression mechanism, and as you heard, a malignancy signal that occurred in a non-human primate.

At the time the drug was approved, there had been 756 patients that were treated with two courses of this drug. The way this drug is given is a 12-week weekly infusion, followed by 12 weeks off drug in order to allow lymphocyte recovery. And so the two cycles of treatment is approximately 48 weeks, or about one year of treatment.

So at that time, there was safety data on 756 patients, and some slightly larger number of patients that had been treated with a single course of this fusion protein.

Efalizumab was brought into psoriasis as an immune-mediated disease, and

at the time of approval, there had been quite a few patients -- more than a thousand that were exposed to a short course of treatment -- but only 218 patients on whom there were safety data for one year of time. And so these are two examples of drugs where the first indication in man is psoriasis, but there is not prior safety data, and where the decisions were made on smaller numbers of patients than you have here.

DR. BIGBY: Thank you. I should mention to the members on the panel that the Agency this year would like for us to have a simultaneous vote as opposed to going around the table and decide who's voting yes or no. So that at the point that I call for a vote, we'll sort of vote with a show of hands. This does not preclude a prior discussion of each question, which we will commence now with question one.

So the first question is, has the applicant provided sufficient information to

demonstrate efficacy of ustekinumab in the treatment of plaque psoriasis? And the floor is open to comments.

I was about to say I really like this, we can go on and vote, but --

DR. HECKBERT: My apologies, Dr. Bigby. So comments and questions, I assume?

DR. BIGBY: Yeah.

DR. HECKBERT: You can hear me now? Yeah, I'm not a practicing dermatologist, but I would ask some of the practicing dermatologists in the group -- my concern would be that if I were a practicing dermatologist, I wouldn't know how to conduct the long-term therapy with this drug. We have information about the first 12 to 48 weeks, but what to do -- this disease goes on for years and years, as we've heard eloquently from people in the public. Will physicians know how to dose it over the long-term?

And then I also have concerns about a lack of information about immunogenicity. We've heard about some of the other biologics

losing their effectiveness over time. We really -- from what we've heard today, we don't have good information about the immunogenicity, and I would wonder, as a physician who wanted to treat patients, what can I tell the patient about what's likely to happen in terms of them becoming resistant to this drug over time?

DR. KATZ: In answer to your question, the way we usually dose -- not having experience with this drug -- whether it be methotrexate, Embrel, whatever, is the patient does well and we gradually decrease the dose, either the interval or the dose. That's how it's generally done. The same thing with topical.

DR. HECKBERT: Do you think that dermatologists will know what to do here, or would it be helpful for your average dermatologist to have some guidance from the sponsor on this over the long-term?

DR. KATZ: The sponsor has shown us that if you stop the drug, it gradually

decreases their effectiveness. It's not a cure. So you would automatically intrinsically know if the patient is clear, you don't want to keep giving the same drugs.

As far as the immune effects, that, we can discuss separately with safety, I think.

So that's a separate question.

DR. BIGBY: This issue is actually one that dermatologists live with all the time, because I mean, most of the studies of almost all the things we used are based on short-term studies. There are very few sort of chronic studies of anything, especially these disorders like psoriasis, atopic dermatitis, so this is a reality for every other comparative drug and it's just a reality of practice.

I think that that will be figured out in clinical practice, and I -- I mean, I think that that's how basically we live in practice.

So other comments?

DR. THIERS: Well, yeah. I'll just echo what Michael said. It's kind of like dosing diabetes. I mean, there's no set dosing regimen for diabetes. You kind of play it by ear, depending on how the patient responds.

DR. BIGBY: So if there's no objection, I'd like to just see by show of hands how many think in the affirmative that the sponsor has demonstrated efficacy of the drug in the treatment of plaque psoriasis.

So if you say yes to this question, raise your hand.

Now, just for my information, the voting starts here and ends with Dr. Shwayder; is that correct? I mean, these are the only people that can vote, though, right?

DR. WALKER: Yes. That's correct.

DR. BIGBY: So now we have to go around, and for each of you that raised your hand, just make a comment about why you voted in the -- so you have to identify yourself

and say why you voted in the affirmative.

DR. SHWAYDER: I thought the data convincingly showed that it worked.

DR. RINGEL: There seems to be a statistically significant difference from placebo, and there seems to be a clinically significant difference.

DR. HECKBERT: Yes, I felt the data showed efficacy.

DR. DRAKE: I think the data showed efficacy.

DR. CRAWFORD: Clear efficacy was demonstrated in the placebo trials. Less clear are the comparisons that were made with the existing (inaudible) because of the different way of looking at it, but it's clearly efficacious.

MR. LEVIN: Did you want names, or not?

DR. BIGBY: Yes, we need to know your name. Yes.

So I guess we'll start over.

DR. SHWAYDER: Tor Shwayder. I thought the data showed efficacy.

DR. RINGEL: This seems very silly. Eileen Ringel. I thought it was a statistically significant difference, and that statistically significant difference was also clinically significant.

DR. HECKBERT: Susan Heckbert. I think the data showed efficacy.

DR. DRAKE: Lynn Drake. Showed efficacy.

DR. CRAWFORD: Stephanie Crawford. Efficacy demonstrated -- less clear in comparison with the existing therapies of the advantages.

MR. LEVIN: Arthur Levin. Data demonstrated efficacy.

DR. THIERS: Bruce Theirs. The data demonstrated efficacy.

DR. BIGBY: Michael Bigby. I was admonished that I'm supposed to give the total. There were 11 yes votes. And if you

look -- if you compare the efficacy in terms of PASI 75 and PASI 90 data for this drug, it's quite striking how well it works compared to other things that we have available.

DR. MAJUMDER: Mary Majumder. Data demonstrated efficacy.

DR. STERN: Rob Stern. Clearly effective in the population studied. Still big questions about whether it does very much -- or how long it works for in a chronic disease and what optimal dosing is, particularly long term.

DR. KATZ: Robert Katz. Unquestionable efficacy.

DR. BIGBY: Addressing the same question, all those that would vote no on this question, raise your hand. So there were no no votes.

So we move on to the second question. And again, it is, the applicant has proposed dosing every 12 weeks. Has the applicant provided sufficient information to

support this dosing schedule?

The floor is open for discussion.

DR. CRAWFORD: Thank you, Mr. Chairman. A point of clarification, please. Would this still be an initial dose then a four-week dose, then after that, every 12 weeks?

DR. BIGBY: Yes. I think you raise an important issue, and I think the FDA's going to have to address this, because at least for the questions that are in front of us, they don't want us to fix the wording of the questions,

So Dr. Walker, you're going to have to tell us what you want to do, because the study actually in the initial treatment period, was every four weeks. So what do you mean by this question?

DR. WALKER: Right. The clarification is consistent with the initial dosing and then the Q-12 weeks. Because there was Q-12 weeks, there was some eight-week dosing, et cetera, et cetera.

DR. SHWAYDER: I have a comment.

DR. BIGBY: Hold on a second.

If you want us to vote with this question, it's going to have to be clearer what it is that we're --

DR. WALKER: If you answered yes to this question, it would assume that after the initial loading doses, or the two doses, that it was every 12 weeks as opposed to every eight weeks, or 12 and then 8, et cetera. I think it's fairly straightforward.

DR. BIGBY: So the question really is about the maintenance dose then --

DR. WALKER: That's correct.

DR. BIGBY: Giving it every 12 weeks. Does that answer your question?

DR. CRAWFORD: I guess I have to ask a point of clarification. We're talking about dosing. Which dosing?

DR. BIGBY: I think it's just -- I think at this point, we're just dealing with the interval for maintenance, and the amount

is to be discussed.

DR. DRAKE: Thank you.

DR. SHWAYDER: My comment is the following: that yes, they showed the Q-12 week for a good part of their study work. I'm always very leery of putting into hard writing something the doctor must do, because we'll probably find some single nucleotide polymorphisms that need every two weeks and some that need ever 52 weeks, and I don't want, at some point in the future, our hands being tied that we have to do it every 12 weeks because that's just the way their initial study did it.

DR. BIGBY: But is there any drug like that?

DR. SHWAYDER: It's more that it should be worded in such a way that it gives the physician -- when the final wording comes out, I would like it worded in such a way that it's recommended rather than mandatory.

DR. BIGBY: Other comments?

DR. KATZ: Yes. Concerning that, to

support what Tor said, we vary that with methotrexate as well. I mean, give it every week, patient's doing well, do it every two weeks. So that's commonly done.

DR. STERN: I guess I interpreted the question differently. It's really, is the evidence they presented sufficient to support a 12-week interval, which is different than what might be the guidelines in clinical practice.

DR. WALKER: That's very clear and very reasonable.

DR. BIGBY: So I think we'll put this one to the vote. So all those that would vote yes on question two, please raise your hand.

We have 11 yes votes? Okay. And people who vote no on this question? And were there any abstentions? So there are 11 yes votes.

For variety, we'll go counterclockwise.

Dr. Katz?

DR. KATZ: Do you want just to state the vote?

DR. BIGBY: I guess you have to say your name again.

DR. KATZ: I think I remember that. Robert Katz. Yes. The variation of the dose will come in the next question.

DR. STERN: The other Robert just took my answer away. Yes for interval. I'm not sure about minimal effective dose for this.

DR. MAJUMDER: Mary Majumder. Yes.

DR. BIGBY: Michael Bigby. Yes.

DR. THIERS: Bruce Thiers. Yes.

MR. LEVIN: Arthur Levin. Yes.

DR. CRAWFORD: Stephanie Crawford. Yes. It seemed pretty consistent with all the data that showed the 12-week mark, that curve started going down.

DR. DRAKE: Lynn Drake. Yes.

DR. HECKBERT: Susan Heckbert. Yes, they did show it for the period of time that they studied it. Yes.

DR. RINGEL: Eileen Ringel. Yes. I think the data did support it. I hope that people read the package and start to see that some incomplete responders needed eight-week dosing.

DR. SHWAYDER: Tor Shwayder. Yes. And I agree with what Dr. Ringel just said.

DR. BIGBY: The third question is, please discuss the alternative weight-based dosing paradigms. Which dosing regimen do you recommend? Obviously, this is not a yes or no one.

The floor is open.

DR. RINGEL: For me, I think we have to decide something first. We have to decide if this drug is going to be given by patients or administered in the doctor's office, because if it's administered by patients, that might be difficult. In a doctor's office, I see no reason why you couldn't use continuous mg/kg dosing. But I think that's something we need to decide on first.