five-plus-year study of adverse events in psoriasis patients in Sweden treated with ustekinumab in actual clinical practice.

There's a 100 percent patient capture in this inception cohort. It will allow potentially 4,000 patients treated with ustekinumab to be followed longitudinally. The ambulatory care, hospital discharge, pharmacy utilization, and the malignancy registers will be combined into a single analytical dataset.

Since the denominator of this database is known, and it captures all psoriasis patients, comparisons of adverse events of interest can be made both by disease and indication with and without ustekinumab exposure.

PSOLAR, another dataset used for signal replication, is an ongoing disease-specific psoriasis eight-year observational cohort study. It is an international multi-center registry that will

expand to approximately 450 sites, with a balance of academic and community centers.

PSOLAR is currently enrolling 4,000 infliximab patients, and 4,000 patients on other therapies -- biologic, other systemic, phototherapy, or topical therapies. We plan to amend this protocol to allow the inclusion and the study of ustekinumab. We propose to enroll an additional 4,000 patients treated with ustekinumab who will be followed for eight years of observation.

In this registry, there is active collection of all serious AEs and other targeted AEs with electronic data case report forms. There is interval longitudinal patient assessment. Extensive data on comorbidities and disease severity are also collected.

PSOLAR's managed by a CRO responsible for monitoring, and one that uses active, quality checks of data, both by the sponsor and by site staff. In addition,

there's a protocol-driven patient retention mechanism in place, and a steering committee that has been instrumental in its design and its implementation.

In contrast to a single product registry, an advantage of PSOLAR is that it can help characterize the pharmaco-epidemiology of moderate to severe psoriasis. By controlling for underlying patient comorbidities, it will be possible to make appropriately adjusted comparisons with adverse events between groups exposed to different therapeutic agents.

In addition, health care databases with record access will provide access to claims and patient level data, including exposure to a drug, the clinical characteristics of the patients, and adverse events of interest.

These datasets complement claims-only databases like PharMetrics to assure a broad capture of patients treated

with ustekinumab. These sources also allow comparisons of adverse events of interest by disease and indication, with or without ustekinumab exposure.

We currently are evaluating a number of potential data and population sources, such as I3.

I have outlined the elements of a risk assessment program to evaluate the stated theoretical concerns. Ustekinumab data resources will allow us to potentially undertake more formal epidemiologic studies that can quantify the strength of the association, the relevant risk factors, and the identification, if possible, of high-risk subgroups.

The final component of the risk management plan is risk minimization. Risk minimization strives to foster appropriate and safe use of ustekinumab. We plan to provide education on the appropriate and safe use, and a care coordination program that

facilitates follow-up with health care professionals.

The proposed ustekinumab prescribing information will include all appropriate safety information. The primary risk minimization activity is the prescribing information. Here are some examples of the proposed safety information highlights in the U.S. prescribing information -- in the warnings and precautions section, in the infections section, caution -- and use in patients with chronic infection or history of recurrent infection -- screening of patients for latent tuberculosis; avoidance in patients with clinically important active infections; caution in use in patients with chronic infection or a history of recurrent infections.

In the malignancy section, immunosuppressive agents have the potential to increase the risk of malignancies -- caution in use in patients

with a history of malignancy, or patients who develop malignancy.

In addition to the prescribing information, physician and patient education programs are an integral part of our risk minimization plan. It is critical to identify the physician segment that will use the drug, to target educational efforts. The education program will focus on dermatologists and associated physician extenders, professionals best able to make psoriasis benefit/risk assessment decisions.

A comprehensive education plan is being developed to address appropriate patient selection, educating on key benefit/risk information, highlighting the need for regular follow-up to assess patients for adverse events, and to provide reminders to dermatologists on their patients receiving ustekinumab.

We propose an education plan and materials focused on theoretical risks as

well, such as serious infections and malignancy. And as part of this plan, we propose to educate dermatologists on the National Psoriasis Foundation Clinical Consensus recommendations for screening and the American Academy of Dermatology recommendations for yearly skin exam.

We also propose a comprehensive patient education program. Patient tools and programs will promote education on potential risks and side effects and how to recognize them, when and who to call with questions or concerns, appropriate technique for administration of ustekinumab, the need for regular follow-up with health care provider to assess for side effects, and appropriate patient follow-up through an individual care coordination program.

I would like to address self-administration of ustekinumab. As a background, subcutaneous biologic agents to treat psoriasis are commonly

self-administered. Ustekinumab has been self-administered under observation in pivotal trials, as discussed earlier in the presentation by Drs. Guzzo and Yeilding, with no difference in efficacy or safety noted in these patients. This data speaks to the question of the patient's ability to self-administer ustekinumab.

The decision on whether the patient should self-administer should be made in concert with the physician and the patient. We propose that the treating physician determine the setting for ustekinumab administration. For the capable and compliant patient, self-administration should remain an option.

Ustekinumab patients should be followed regularly by their physicians as recommended in the AAD guidelines and NPF consensus documents. To help ensure appropriate patient follow-up with their physicians, we propose an individual care

coordination program. This program would have coverage throughout the United States, and the centerpiece of the program is regular, personal contact with the patient prior to each scheduled treatment. This will prompt the patients to schedule follow-up visits with their dermatologists, provide a reminder to the patient of their next scheduled dose; it will be able to deliver patient education tools with every treatment. And perhaps importantly, provide reminders to the dermatologists on their patients receiving ustekinumab.

In addition, Centocor will provide hotline support for any questions or issues that may arise.

There are advantages and disadvantages associated with a mandatory registry. In a mandatory registry, all individuals exposed to the drug are captured, with the ability to obtain longitudinal data on each patient. These data tend to be

limited to the events of interest. Perhaps most importantly, a mandatory registry does not contain a comparator cohort. Patient retention problems exist, making longitudinal follow-up with patients who withdraw from the registry problematic.

Without a proposed risk management plan, comparison cohorts are available for analysis. There are patient retention programs in place for PSOLAR, and with our similarly designed registry in Crohn's disease, we see attrition rates that are approximately 8 percent per year.

Longitudinal data is captured in PSOLAR, in our Nordic database imitative, and in health care datasets with access to medical records, but perhaps most importantly, the use of comparator cohorts gives us the ability to corroborate a signal against event rates in the non-ustekinumab-treated patient population, assuring that the potential risks can be

evaluated in context.

Based on the comprehensive nature of our risk assessment program, a program modeled on the FDA's own Sentinel initiative, and our goal of assuring that we effectively monitor the safety of ustekinumab, we believe that our risk assessment proposal has compelling advantages over a mandatory registry of ustekinumab-treated patients.

In conclusion, we propose to launch new and to augment current prospective observational cohort studies; to enhance ustekinumab risk assessment; to conduct targeted risk assessment as specific safety issues arise; and to implement measures that will inform and educate both physicians and patients on the benefit/risk profile of ustekinumab.

The use of these measures will allow for the safe and effective use of ustekinumab post-approval. Thank you.

I'd like to introduce Dr. Mark

Lebwohl, chairman of the Department of Dermatology at the Mt. Sinai School of Medicine.

DR. LEBWOHL: Thank you. I am here to tell you why we need additional systemic therapies for psoriasis.

This is the list of oral treatments currently approved for psoriasis, and I'll point out first that none of the treatments on this list have been subjected to the thousand-plus patient pivotal trials that are required of the biologics. Some of these are dramatically effective but have their limitations.

Methotrexate, for example, is associated with hepotoxicity, and guidelines for methotrexate call for periodic liver biopsies in patients on chronic therapy. Probably, its most serious side effect, however, is bone marrow suppression, and every year there are cases of pancytopenia and death in patients treated with low dose

long-term methotrexate.

For cyclosporine, guidelines call for limiting the use of this drug to one year, because kidney damage occurs in patients treated for longer. Acitretin is a drug that by itself has limited effectiveness and is also associated with numerous mucocutaneous side effects and is teratogenic. For that reason, it's often used with phototherapy, which requires visits several times per week.

PUVA, Dr. Stern has shown, is associated with an increase in squamous cell carcinomas and malignant melanomas.

This is the list of the biologic agents currently approved for psoriasis. Alefacept, the first of these approved, achieved PASI 75 in 21 percent of patients at week 14, and for that 21 percent of patients was a very effective drug, but, unfortunately, a high proportion of patients do not achieve that degree of improvement.

It's also associated with a reduction in CD4 cells, and you'll see for every drug on the list of biologics -- and also should have applied to some of the oral agents we showed as well -- infection and malignancy listed is potential side effects, because they all effect the immune system.

Efalizumab achieved PASI 75 in 27 percent of patients at week 12 and its associated with flares of psoriasis, thrombocytopenia and additional side effects. The TNF blockers are associated with a long list of side effects, such as the predisposition to tuberculosis reactivation, worsening of demyelinating disease.

And I'll point out that the most effective of these, infliximab, is associated with infusion reactions in a significant proportion of patients.

For those reasons, we need additional psoriasis therapies. Many of the therapies currently available do not achieve

PASI 75, and many of the ones that do lose that effectiveness over time.

I've already elaborated some of the safety concerns we have about other systemic therapies for psoriasis. And most importantly, psoriasis is a lifelong disease that requires sustained remissions for long periods of time.

This is a summary of the treatments that our patients enrolled in this trial had been on, and many of them had failed. You see that two-thirds, nearly, of patients had received either phototherapy with UVA or UVB. That's PUVA or UVB. Over half the patients had received conventional oral systemic therapies that I just reviewed. And 43 percent had been treated with one or more biologics.

The pie chart that I'm showing you here is the result of a survey that was sent out to members of the Psoriasis Foundation.

Over 11,000 responded. And what

you see here is that over three-quarters of patients report either fluctuation or worsening of their disease. And one of the greatest fears of patients with severe psoriasis, even those who are adequately controlled with the treatments they're on, is that their psoriasis will recur. So we need a treatment that will give sustained clearance -- the kind of remissions that we are seeing with ustekinumab. This is a patient at baseline and follow-up at week 52, and I'll just point out for those of you who are quick at math that this patient did not have a PASI 75 at week 52, but look at the dramatic improvement.

Here's a patient again treated with the 45mg dose at baseline and week 52. And again, here's a patient treated with 90mg at baseline and week 52.

So what ustekinumab offers is a novel alternative mechanism of action, a high efficacy that we have never seen before with

only one or two subcutaneous injections, a maintenance of response of months with only one or two subcutaneous injections that we have not seen before -- convenience with every-12-week injections, the ability to adjust dose based on the patient's weight, and a good safety profile through 19 months.

And I will say that this is the first drug where the pivotal trial -- the first psoriasis drug where the pivotal trial required follow-up of all patients enrolled for five years in addition to the standard and more-than-standard post-marketing surveillance. So I ask you to approve this dramatically effective drug for psoriasis.

Thank you.

DR. BIGBY: I would now like to open the floor to people sitting on the panel for clarification questions to the sponsor. I would urge you not to start the discussion of the question though in this question and answer period.

DR. CRAWFORD: Thank you, Mr. Chairman. I'm Stephanie Crawford. These questions are directed to Dr. Yeilding and Dr. Callegari.

First one, Dr. Yeilding, if I heard you correctly, most of the patient subjects that were studied in the clinical trials were in their third or fourth decade -- in other words, is there little data available on use of the drug in elderly patients? And if so, how do you propose to provide more data?

That's the first question.

For Dr. Callegari, as an academic, I'm very attuned to when I hear declarative versus speculative statements, so with the enhanced risk assessment plans, I heard a lot of "might," "could," "may." Would you please clarify what is the commitment of the sponsor to all those aspects of the new risk assessment plan?

DR. YEILDING: Thank you for that question. I'll first address your question of

subjects in the third or fourth decade of life. I may not have been clear on that. At that point, I was discussing the theoretical risks of blocking IL-12 and 23 -- in patients that have been identified that are genetically-deficient in IL-12 and 23 or their common receptor -- these patients are generally younger patients that are not older than the third or fourth decade of life.

That's to be distinguished from our clinical trial population. And if we can have the slide up here, you can see here that the mean and median age in our clinical trial is in the mid-forties. We had patients that ranged anywhere from 18 years of age to 86 years of age. So we have a broad representation in terms of age distribution.

DR. CALLEGARI: In terms of your question, there was no intent for equivocation. We will commit to these. The reason that I'm not definitive about the datasets themselves is that we need to explore all the additional

datasets to make sure we've identified ones where ustekinumab uptake is going to be sufficient enough for us to be able to detect a signal.

One of the challenges with claims datasets or health care datasets is that they're very dependent on formulary issues. And so if the formulary doesn't approve ustekinumab, even if I have 50 million people covered, if none of those people are going to receive ustekinumab, it's not a very useful dataset for me.

And so that's the reason -- and I apologize if it came across as equivocation.

DR. BIGBY: Bob?

DR. STERN: Yeah. One of the speakers mentioned about Centocor's proven record in terms of post-marketing surveillance, and I'd like the numbers in terms of enrollment in PSOLAR, which has been going for some time now. It was a much earlier commitment for infliximab. How many people were enrolled? How many people

you have definitive direct contact with those individuals at six months and a year -- both among people who received infliximab and other individuals? Was it three years since that commitment?

DR. CALLEGARI: No, it's one year since that commitment for PSOLAR. And the steering committee for PSOLAR, a steering committee that's composed of academics and clinicians, had mandated that we needed to test the electronic data capture forms before broadly launching the registry -- so the initial release of user acceptance tests that involved 30 sites has been completed. The revised forms are now active. With the initial release, the current enrollment is 485 patients. We'll expand investigator sites outside of the 30 to 75 to 100, and over the next year to 450.

By the end of 2008, we'll anticipate 1,000 patients enrolled, and by the end of 2009, we'll have over 5,500 patients enrolled.

In terms of other regulatory commitments, we have successfully enrolled a 5,000 patient registry on time for Crohn's disease called TREAT. We have successfully enrolled a 5,000 patient registry in rheumatoid arthritis, and we've met other regulatory guidelines. We've had first patients -- again, for our pediatric Crohn's disease registry in a commitment in a timely fashion, so we have had a timely fashion for these.

DR. STERN: When was infliximab approved for psoriasis? 2005, was it?

DR. JONES: Six. Six.

DR. STERN: 2006. So in two years, you've enrolled 460 individuals -- with no follow-up, as I understand it. Basically, it's taken two years to get to that point.

DR. CALLEGARI: It has taken two years to get to 450 patients, yes.

DR. BIGBY: I have a couple of questions. For Dr. Guzzo, on slide 46, where

you pick the 12-week cutoff point based on weight, I just need to know, what is the number in each of those figures?

DR. GUZZO: Could you bring up slide 46, please?

DR. BIGBY: What is the end number of patients in these studies?

DR. GUZZO: In this study, 320, with approximately 60 patients per treatment group.

DR. BIGBY: Also, in slide 59.

DR. GUZZO: If you could bring up 59, please.

DR. BIGBY: When the placebo group was crossed over, did they get an injection at 12 weeks?

Was that the zero for them? They got an injection at 12 weeks, 16 weeks, and then it was every 12?

DR. GUZZO: Correct.

DR. BIGBY: Okay.

DR. GUZZO: So they mimicked the initial group and then went on every 12-week

dosage.

DR. BIGBY: For Dr. Yeilding, you mentioned that patients that have a genetic defect in IL-12 or the p40 segment -- at what rate do they get salmonella and mycobacterial infections? What percentage of them actually had those infections?

DR. YEILDING: I'm going to ask one of my colleagues to come to the microphone and address that question -- Dr. Michael Elliot -- who's the senior vice president of our clinical R&D immunology group.

DR. ELLIOT: Thank you, yes. Those individuals are of course rare. The case series now include around 150 individuals, and the individuals are identified because they present at an early age with an unusual infection, a mycobacterial or salmonella infection.

Now interestingly, when genetic studies have been done on the siblings of some of those affected individuals, it is found that the penetrance of the phenotype is

limited. So putting that another way, there are individuals who are genetically-deficient who do not appear to present with the infections. The data are fairly limited, but the penetrance is estimated at around 40 percent.

DR. BIGBY: This is my last question for Dr. Callegari. What do you intend for pregnancy labeling for the drug?

DR. CALLEGARI: Actually, I'll ask Dr. Jones to address that question.

DR. JONES: Right. We are proposing pregnancy category B -- developmental and reproductor tox (?) studies have been performed in cynomolgus monkeys the dose is up to 45 times the recommended clinical dose of ustekinumab. These studies have revealed no evidence of harm to fetuses due to ustekinumab. So this goes on to describe other studies have not shown any adverse findings.

DR. BIGBY: Dr. Heckbert?

DR. HECKBERT: Yes. I have some

questions to follow up on Dr. Crawford's questions. This drug ustekinumab is not approved anywhere right now, or in any of the European countries; correct?

DR. CALLEGARI: That is correct.

DR. HECKBERT: Right. So can you tell me -- but infliximab has. So my question would be, how many people use infliximab in Finland, Sweden, Denmark -- my question is, what has been the uptake of that drug in those countries -- just to give us an idea of how readily those countries are likely to use the biologic therapies?

DR. CALLEGARI: Over 10,000-plus patients are on infliximab in those three countries.

DR. HECKBERT: And the data on those patients would be available in those registries?

DR. CALLEGARI: Yes.

DR. HECKBERT: Is that for psoriasis? That's for the combined -- for lots of different indications?

DR. CALLEGARI: That's for the combined indications.

DR. HECKBERT: Is what you're proposing to follow people with all indications that might receive biologics, or just to follow people with psoriasis?

DR. CALLEGARI: We propose to follow people with psoriasis who were receiving other therapies as well.

DR. HECKBERT: So what proportion of those 10,000 are receiving infliximab for psoriasis?

DR. CALLEGARI: Probably 1 percent.

DR. HECKBERT: One percent of the 10,000?

DR. CALLEGARI: Yeah.

DR. HECKBERT: So there hasn't been a whole lot of uptake just yet.

DR. CALLEGARI: Of infliximab for psoriasis. However, there has been obvious uptake of other biologics for psoriasis in Europe.

DR. HECKBERT: I see, and what other ones are you talking about there? What other agents?

DR. CALLEGARI: Countercept (?)

DR. HECKBERT: For psoriasis? Okay. So what is the total number of people being treated with biologics for psoriasis in those databases, would you estimate?

DR. CALLEGARI: The total number -- as I said -- excuse me?

It's probably about 1,000 for psoriasis patients.

DR. HECKBERT: 'm just trying to get at the issue of how much power you have there.

DR. CALLEGARI: Right.

DR. HECKBERT: How much power you have there. Then moving on to the PSOLAR initiative, I don't feel like I have much information about that initiative overall. You're asking dermatologists, I assume, to participate in this registry?

DR. CALLEGARI: We are asking

dermatologists to participate in the registry. There is a steering committee composed of academic community sites that have full access to the data, full access to any analyses, and no analysis will go public without full approval by the steering committee.

DR. HECKBERT: What kinds of incentives are there for physicians or patients who participate in the registry?

DR. CALLEGARI: There are no patient incentives, and physicians are compensated for their clinical trial efforts alone.

DR. HECKBERT: That's on a per patient basis?

DR. CALLEGARI: It's as a normal clinical trial -- recognized that Remicade patients as well as other patients are enrolled in it, so there's no differential compensation for that.

DR. HECKBERT: I guess physicians are encouraged to enroll all their patients regardless of what treatment they might --

DR. CALLEGARI: It is a disease-specific registry, so we would prefer to capture as many patients -- both treated and not treated.

DR. HECKBERT: At the present time, what proportion of patients enrolled in PSOLAR are getting biologics versus systemics versus other treatments?

DR. CALLEGARI: I might actually ask my colleague, Dr. Keenan, who's more intimately familiar with that number, to come up.

DR. GUZZO: One thing that I would point out about infliximab -- it's an IV-administered agent, and therefore does have some limited uptake in the dermatology community compared to subcutaneously administered agents for psoriasis.

DR. KEENAN: My name is Greg Keenan, and I oversight the medical affairs-sponsored research at Centocor. So currently, we have approximately 485 patients in the PSOLAR registry. Approximately a third of those

patients are receiving infliximab.

DR. HECKBERT: And the others are --

DR. KEENAN: At this point, the PSOLAR registry inclusion criteria include those that are appropriate for systemic therapy.

DR. HECKBERT: So presumably, the other two-thirds are receiving systemic therapy or are off therapy?

DR. KEENAN: They're appropriate for systemic therapy. That was the inclusion criteria. And the idea there is to get a broad-based population from which to draw comparison cohorts.

DR. HECKBERT: Okay. Thank you.

DR. BIGBY: Dr. Katz?

DR. KATZ: Dr. Guzzo, you said that the average extent of psoriasis was 20 percent. How small a percentage did that go to? What percentage of patients had 10 percent or 5 percent --

DR. GUZZO: So the lowest that you could have to be in the study was 10 percent.

DR. KATZ: Thank you.

On table 72, was any consideration given to patients -- you addressed very well the 70 to 100 kilo patients, but how about less than 50 kilo patients? Or 50 kilo patients who had 100 percent response to both the 45 and 90mg dose? Was any consideration given to a lower dose for that group of patients?

DR. GUZZO: We did not test a lower dose. The number of patients who entered the 50 -- slide up, please. As you can see, the number of patients who are less than 50kg is small -- 7 and 6, 13 patients. So that would be a very low percentage of patients in that weight range.

DR. KATZ: So they'd be obliged to be taking the 45mg dose despite that fact that as far as we know, they might respond as well to half the dose?

DR. GUZZO: Well, that is true. They will get a higher dose, but to date, we haven't

detected safety signals -- even with 90 versus 45 -- or even as Dr. Yeilding showed you, when we look at lower-weight patients who get the highest dose, we don't see a difference in their safety signals.

DR. KATZ: My last question is, it is almost implicit in the literature that these drugs are marketed to moderate to severe, whereas moderate is defined as 10 percent. So the insistence on using that term for 10 percent of body involvement -- perhaps the non-dermatologists should know that's like one extremity. Would consideration be given to use in patients with severe involvement, since it's a potentially severe drug?

DR. GUZZO: As you know, aside from the biologics, aside from infliximab, the biologics are approved for moderate to severe psoriasis. That is the population we studied, and we do believe that the safety profile supports moderate to severe indication.

I'd like to ask my colleague

Dr. Alexa Kimball to comment, and then Dr. Lebwohl on the classification of psoriasis. As you well know, there is a lot of overlap, and many other things come into consideration for classification of moderate to severe other than just body surface area.

Dr. Lebwohl.

DR. LEBWOHL: Not to confuse the non-dermatologist members of the committee, one extremity would be 9 percent -- if 100 percent of the extremity was covered. That would be 9 percent of the body surface area. And that usually doesn't happen, so when you have a patient with 10 percent, they've usually got psoriasis that is scattered on several body sites, not limited to -- you know, if somebody has psoriasis on the elbows, that's not 10 percent of the body surface area or 9 percent of the body surface area.

So 10 percent I think accurately is moderately severe. Severe enough to have many of the emotional impacts that you heard

Alexa describe. Think of it: if you have psoriasis involving your palms, just the palms of your hands, that's 2 percent. And think of how debilitating that is to patients who have the palms of their hands affected, or their soles, the soles of their feet, affected.

DR. KIMBALL: Just to sort of draw out one of Mark's points, it's not as if there's one spot to treat. When you have 10 percent body surface area, you probably have 20 or 30. On average, a patient with topicals spends 26 minutes a day treating with topicals.

From a very intuitive standpoint, when I first started doing studies and saw criteria such as 10 percent body surface areas -- I have to say it was very intuitively reassuring, because those were the patients who walked in the door who clearly could not manage their disease with topicals alone, and I think that is a very legitimate boundary to start considering the

other therapies and the whole picture to see if they'd be appropriate for treatment, but they really cannot be managed just by putting on creams.

DR. BIGBY: We're going to go into the break now, and it'll be 15 minutes. We'll reconvene at 10:30.

(Recess)

MS. WAPLES: Hello. Will you please take your seat? We're about to begin.

DR. BIGBY: We're going to go on to the FDA presentation. I'd like to just reassure the people on the panel here that people who have questions for the sponsors, we'll find time for you to get your questions and clarifications made. It will either be at the end of this session or before we start deliberation.

So let's go on to the FDA presentation.

MS. FRITSCH: Good morning. My name is Kathleen Fritsch, and I am a biostatistician

at the FDA, and I will be presenting some more information on the efficacy of ustekinumab, with special emphasis for maintenance dosing.

The two Phase 3 studies were previously introduced by the applicant, T08 and T09 -- the 12-week studies with the placebo control period, followed by crossover dosing. The follow-up period for the studies was 52 weeks for the first study and 28 weeks for the second study. And for the efficacy endpoints, the PASI 75 and the PGA of cleared or minimal.

I'll just briefly go over the efficacy at week 12, which was the primary time point. As previously discussed, the efficacy is around 60 to 70 percent on the two active doses, and statistically significant.

I'll spend the majority of my time talking about the maintenance dosing. I'll first look at the periods from week 16 to week 28. We have information for both

studies in this time frame.

The study design was to have the initial period with the two initial doses followed by dosing at week 16 for those on the active arms, and the crossover dosing for those on the placebo arm. And this period represents the relatively complete follow-up for the subjects -- the additional randomization determined the dosing during this period.

The efficacy response -- again, this was previously presented -- generally in the range of 70 percent throughout this dosing period for both doses. And here's the second study. In general, from here on, I'll be talking about the PASI 75 response.

I'll spend a little bit more time on the next phase of these studies, which was the week 28 to week 52 period. And for this period, we have data only from study T08. I'd like to go a little more into detail about exactly how the dosing was conducted

during this phase of the study. At this point, subjects were re-assessed, and based on their efficacy at week 28 were assigned into three groups -- those who were non-responders, those who had less than 50 percent improvement on their PASI were discontinued from this study and not treated further -- partial responders: 50 to 75 percent PASI improvement were accelerated to dosing every eight weeks; and the responders: greater than 75 percent improvement in PASI were continued on the 12-week dosing. And these subjects were then re-assessed at week 40.

So those that responded and were continued on the week 12 dosing, if they slipped back into non-response or partial response, they were at week 40 then accelerated to every eight-week dosing, and if they were responders again at week 40, then they were entered into either the randomized withdrawal period, which was to

continue every 12-week dosing or withdraw treatment.

Here's the schematic showing all the phases. We have the initial 12-week period, followed by the maintenance and crossover phase through week 28. Then as I mentioned, there were three choices at week 28 -- either discontinued, accelerated to every eight-week dosing, or continued on the every 12-week dosing for both treatment arms.

And finally, for those who had been continued on the week 12 dosing, they were either continued on 12-week dosing or withdrawn from treatment or accelerated to every eight-week dosing.

So just to give the full picture of the study design and treatment regimens used through week 52.

The proposed dosing regimen is every 12-week dosing after the initial two doses at the baseline and week four. So I'll

simplify this diagram here to look back at the number of subjects that we have followed for the every 12-week dosing.

So in this study, we had roughly 250 subjects per treatment arm. Most of those subjects were followed for the first dosing maintenance dose. Then the responders were continued here, and the responders comprised about 180 subjects per group. And then of those responders, about 150 were still responders at week 40.

And of that group, half were continued on every 12-week dosing. So we have roughly 80 subjects that were continued on the dosing through the entire one-year period.

So there's the number of subjects that we have for more than one maintenance dose.

To see how many subjects were on the accelerated dosing, just to see how everyone was followed up, at week 40, which

was the last time point where subjects switched regimens, the first two groups here are those that were responders at both weeks 28 and week 40. That was about 67 percent of the subjects.

Half of those were randomized to receive the last dose at week 40, and half were randomized to withdrawal treatment at week 12. About 22 to 28 percent of subjects were accelerated at either week 28 or week 40 to the every eight-week dosing.

2 to 7 percent of subjects were terminated at week 28 for non-response. And of course, every study has a certain percentage of dropouts. In this case, we had about 6 to 9 percent of subjects who dropped out by week 40.

Looking at how the efficacy was maintained, during the week 28 to 52 week period in study T08 -- again, I believe this diagram was shown previously by the applicant. We followed the responders at

week 28. The graph on the left shows week 28 to week 40. By the end of that dosing period, about 90 percent of the subjects were maintaining response. These subjects were then followed to week 40 to 52 week period, and they were randomized to either withdrawal or continue dosing.

Again, 87 to 91 percent of those subjects maintained dosing, and fewer subjects maintained dosing after the withdrawal -- though it is notable that 60 percent of the subjects were maintaining efficacy a full 24 weeks after their last dose.

So just a summary of the number of subjects that have been followed through week 52 for these studies. We have about 650 subjects initially randomized. Most of those subjects were followed for one maintenance dose, and about 180 subjects per treatment arm for the second maintenance dose, and about 80 received the third maintenance dose.

And these groups represent the people that have responded at week 28 -- and also here responded also at week 40.

So in summary, we have the every 12-week dosing regimen was continued past week 28 only in subjects who were responding at the key time points of week 28 and 40. We don't have the information -- the information presented here then does not represent subjects who may have slipped back to partial response, because those subjects were all accelerated to more-frequent dosing regimens, and other maintenance strategies such as looking at longer intervals or looking at lower doses were not evaluated in these studies.

The next speaker is Pravin Jadhav.

He is a pharmacometrician at FDA.

DR. JADHAV: Thank you, Dr. Fritsch. Good morning, Mr. Chairman, members of the committee, representatives from the sponsor, and the FDA and the audience.

My name is Pravin Jadhav. I work as a pharmacometrics reviewer at the Office of Clinical Pharmacology, and what I am going to present to you is our analysis and evaluation of the dosing proposal given by the sponsor using exposure response analysis.

For my presentation I plan to show you for us to establish exposure/response relationship between ustekinumab exposure and response. I'm going to use PASI 75 as one of the response variables. Then I would like to establish relationship between ustekinumab exposure and body weight. Given these two relationships, the exposure response and exposure body weight relationship, I will show you our analysis and assessment of dosing strategy. And the main emphasis is to maximize the efficacy of ustekinumab.

To begin with, I've used data from T08 and T09 trial, which had 1331 patients for 45mg ustekinumab and 90mg ustekinumab-treated patients, and 665

placebo-treated patients. The analysis that I'll show you will involve analysis of PASI 75 and PGA end point, but as I said, I will focus on PASI 75 as the response variable at week 12, which you know was assessed after two doses -- that is week zero and week four dosing.

While I'm presenting this, I would like you to keep in perspective the dosing proposal -- that is, for our labeling purposes, they would like to recommend a 45mg dose to less than 100kg patient, and a 90mg dose to greater than or equal to 100kg patient based on the data that we observe.

Here is a relationship between PASI 75 and ustekinumab exposure. What you're looking at is proportional PASI 75 responders on Y axis and observed ustekinumab exposures on X axis. The placebo-treated patients are plotted at concentration equal to zero, and as you note that the proportion of PASI 75 responders increases with

ustekinumab exposure.

The numbers represent number of patients that have contributed to each of the point on the graph, and the point I would like you to take from here is from patient perspective -- to maximize efficacy, it's preferable to be in the last three quartiles than being in the lower exposure range, and that's where our analysis will focus.

So when we were looking for the characteristics of patients who are in the high concentration range versus low concentration, we found -- and as already presented by the sponsor -- that it was the heavier patient.

What you're looking at is the observed ustekinumab exposures on Y axis and body weight on X axis. The body weight is divided into four quartiles. The 90mg dose is shown in green and 45mg dose is shown in yellow. What you'll notice is that there is a deep (inaudible) with respect to body

weight for concentrations, such that the lighter patient which I defined as median body weight of 68kg patients, could have exposure twice as that of the heavier patients, which I define as median body weight of 117kg. So there's almost twice the difference for a given dose.

You'll also notice that for concentrations at 45mg for lighter patients, is almost equal to concentrations on 90mg for heavier patients, which our sponsor has already made the point.

So given that we have these two relationships, exposure-response relationship and exposure-body weight relationship, it was obvious that there will be a relationship between the proportion of PASI 75 responders and body weight. Again, body weight is divided into quartiles, and a 45mg dose in yellow and a 90mg dose in green.

You'll note that on 45mg, the response rate for lighter patients is about

80 percent versus almost 50 percent for the heavier patients. Also for 90mg, the response rate in a lighter patient is higher than response rate in heavier patients.

I would also like to point this out, that there is a continuum with respect to the exposure of the responder-body weight relationship, which is very similar to the relationship that we see with respect to pharmacokinetics.

So given this relationship -- and we have a dosing proposal which was not actually studied in the trial -- we would like to evaluate what other dosing regimens are possible, with the aim that we can maximize efficacy. So what we did is we doubled up an exposure/response relationship for ustekinumab. You're looking at proportion of PASI 75 responders at week 12 on the Y axis, and the ustekinumab AUC on X axis, where dots represent the observed data, and these lines and shaded area represent the

median and the 95 percent confidence interval for the model.

The point I would like you to take from this slide is that the logistical regression model that was doubled up here reasonably predicts the observed data. And given this model we have, we can also note that somewhere at AUC of 200 and above is that -- again, a threshold I was talking about that is preferable to being the higher exposure rates for efficacy purposes. So we evaluated both -- based on this model -- different dosing regimens.

Now, the question is what are the different regimens possible for ustekinumab? One of the dosing regimens that we considered is one dose for all at 45mg, or you could recommend a 90mg dose for all for ustekinumab. And these dosing proposals are in fact studied in clinical trials. We know from the empirical evidence, post-doc (?) evidence, that there is a body weight

relationship.

So the sponsor's proposal -- which is shown here -- that 45mg for less than 100kg patients, and 90mg for greater than 100mg patient -- is consistent with data.

However, we were interested in, how can we maximize this further? Is there a possibility of getting slightly higher response rate by administering a different dosing regimen? So we considered several proposals, and I'm going to show you only one proposal, which is a three-step proposal, where we evaluated 45mg dose for up to 70kg patient, and 70 to 100 will get a median dose, a mean dose, of 67.5mg, and then the matches to the two-step dosing proposal, where body weight greater than 100kg will get a 90mg dose.

And the idea was to approximate the continuous milligram per kilogram relationship. That is, because we know the pharmacokinetics is dependent and has a

continuous relationship with body weight and it does translate into the response rate.

So here are the results based on the model and the different dosing regimens that we evaluated. If you were to administer the one dose for all strategy, 45mg or a 90mg, we see that we have a difference of about 10 percent response rate, 65 versus 75, but the majority of that difference is driven by greater than 100kg patient, which have empirical data for.

So if we were to administer, which is recommend -- the sponsor's weight-based dosing regimen which gives less than 100kg a 45mg dose, and greater than or equal to 100kg gets 90mg dose, we can maximize the response rate from 54 to 70 percent because we changed the dose in this subgroup.

However, note that there is a possibility of further maximizing response in other subgroup, so we instead of 90 median dose for 70 to 100kg patient -- and the idea

is if we can get similar response rate with the lower dose than 90, why not?

So the model, we can improve the response rate from 65 to 73 percent versus 70 percent in a two-step proposal, and the improvement really happens in 70 to 100kg patients, an improvement of 68 to 74 percent.

So from committee, we are seeking input on what are the advantages and disadvantages of the different dosing strategy -- that is one dose for all, either 45 or 90, a two-step dosing proposal, a three-step dosing proposal. What, from patient's perspective -- and again keeping in mind maximizing the efficacy, what are some of the advantages and disadvantages of this proposal?

So finally, I hope I have shown you that psoriasis improvement is dependent on ustekinumab exposures, and the exposures, the serum concentrations, AUC, are dependent on body weight so that the lighter patients have

more concentrations than the heavier patients. And it does translate into the response rate, so that the psoriasis improvement in heavier patients, the response rate is lower than in lighter subjects.

So from our perspective, the weight-based dosing regimen should maximize the effectiveness. I thank you very much for your attention, and with that, I would like to welcome Dr. Jiaqin Yao, from our pharmacology toxicology division.

Thank you very much.

DR. YAO: Thank you. Good morning. I am Jiaqin Yao, pharmacological reviewer at FDA. Today, I would like to talk about non-clinical evaluation of human monoclonal antibody ustekinumab. First of all, I'd like to talk about the nonclinical evaluation for small molecules and the biologic. General toxicology in two species require recommendation for both small molecules and the biologics.

However, general toxicology in one

related relevant species is acceptable for biologicals. And also based on the naturals biological, immunotoxicology is a required tool of evaluation for the biological.

As far as for reproductive toxicology, one single embryo-fetal development in toxicology are required for biologic. However, for other reproductive toxicology such as fertility study and the pre- and the post-natal studies, sometimes (inaudible) can be incorporated with a single (inaudible) productive toxicology studies.

For genotoxicology for the small molecules -- a battery of three assays are required. However for the biological genetical toxicology study are not recommended generally.

For the carcinogenesis for a small molecule, typically use chronic in human are two chronic carcinogenic studies are required for the small molecules.

For the biologic, however,

historically no carcinogenic study has been submitted to FDA.

As far as ustekinumab, the sponsor has done a program -- non-clinical studies for the pharmacodynamic activity studies as well as tissue reactive (?) studies show that cynomolgus monkey was relevant species for non-clinical evaluations.

For the TK studies, the half-life in the monkeys, two to three weeks, is similar to what happens in patients after clinical use. For the genetic toxicology response, there has not been any studies because for the ustekinumab is biological, it's unlikely to go into the nucleus to react with DNA, so that is not a concern.

The sponsor has done some general toxicology for two GLP studies. One is IV studied weekly for four weeks. Another is 26 weeks, twice weekly up to 45mg per kilo. No significant adverse effects were noted in those studies. However in 1 out of 8 male

monkeys given 45 mg/kg was noticed have infections at week 26. That is 1 out of 8 males or 1 out of 16 monkeys, including the male and the female.

For the developmental and the reproductive toxicology studies, the sponsor has done four different types of studies, including the male fertility studies, two embryo-fetal development toxicology study, and the one combined embryo-fetal and pre- and post-natal development toxicology studies.

The sponsor also did one study in mice using analogous antibody to test the female fertility studies. No significant adverse effect was noted for the dose up to 45mg/kg subcutaneously twice weekly.

Some major concern is carcinogenesis. Non-clinical carcinogenic study has been done with ustekinumab. Since ustekinumab is an immunosuppressant agent, the risk of malignancy is a concern for

patients. Generally speaking, immunosuppressant agents have the potential to increase the risk of the malignancies. From the literature data, we can find that at the administration of IL-12 proteins to the mice which has been challenged with tumor cells or in the tumor models, we can see that IL-12 have anti-tumor effect.

And the literature data also shows that -- although as the sponsor point out, IL-12 and IL-23 may have a definite role in the carcinogenesis, but in the knockout mice, which is knockout IL-12 and IL-23 p40, and also in the mice are treated with antibody against the IL-12/23 p40, the host defense to the tumor is decreased.

Here is one data I can show you that from the literature -- see here, compare with controls here. If treated with IL-12/23 p40, the tumor incidents were increased after the mice challenger (?) with PDV tumor cells, and also the size here -- the tumor size is

greater compared with the controls.

In another study, if the mice challenger was EP2 or breast cancer cells, the tumor size were also increased compared with the controls. So those data suggested that in mice, if challenged with -- if treated with the IL-12 and IL-23 p40 antibodies, the host defense, the tumor will decrease.

As far as other biologicals approved for psoriasis, we can find that they are for the antibody against the CD11a and the CD2, also TNF alpha blockers -- there's no carcinogenic study has been submitted before the approval -- and in one antibody against the CD2, in the nonclinical chronic study, we find that the B-cell lymphoma was noted in one monkey at week 28.

So far, nonclinical study has been done on ustekinumab, there's no positive carcinogenesis signals.

What we can see that -- from the

literature, we can see that there's an association between the inhibition (?) by IL-12 and IL-23 with increased risk for the carcinogenesis in the mice.

Therefore, long-term administration of ustekinumab may have the potential to increase the risk of the malignancy in the patients, particularly for those patients that have been treated with UVB or phototherapy or other immunosuppressant agents.

So based on the positive signals from the literature, the information about the carcinogenic potential of ustekinumab should be incorporated into the labeling.

Thank you.

Now I would like to introduce my colleague, Dr. Carr, to talk about some safety concern. Thank you.

DR. CARR: Thank you. Good morning. My name is Brenda Carr. I'm a medical officer with the Division of Dermatology and Dental

Products with the FDA. I will be talking about select safety concerns with ustekinumab in the treatment of psoriasis.

The talk will cover three topics, the first of which is the assessment of the safety database. It will be broken into the adequacy of the database -- and secondly, the proposed assessment of long-term safety. The next topic of discussion will be the self-administration of therapy. And lastly, immunogenicity of the product.

Assessment of safety. The integrated safety database pooled data from three studies in which 45mg and 90mg doses were evaluated. Each of the studies had follow-ups of different durations, and additional safety data were submitted for the Phase 3 studies T08 and T09, which made for follow-up through 76 and 52 weeks respectively.

The duration of exposure was based on the interval between the first and last

doses of product. Subjects were considered to have had at least six months' exposure if the interval was 14 weeks -- a year of exposure if the interval was 38 weeks, and 18 months of exposure if the interval was 18 weeks.

So for the 45mg dosing group, 994 subjects were considered to have had at least six months of exposure -- 645 at least a year of exposure -- and 187 at least 18 months of exposure. And the numbers are similar for the 90mg dosing group.

The issues to consider -- the applicant has presented an overview of the safety profile; however, the issues to consider in regard to the adequacy of the database to support approval include the adequacy of its size to detect low-frequency adverse events, the adequacy of the duration to detect long-latency adverse events, and the adequacy of size and duration for first-in-class new molecular entity with a

carcinogenicity signal in the literature for treatment of psoriasis, a non-life-threatening condition for which numerous therapies exist.

For the assessment of long-term safety, the applicant has proposed a registry of 4,000 patients to be followed for at least eight years. Additionally, the subjects in the Phase 3 trials will be followed for five years.

The applicant proposes the same plan for ustekinumab as is in place for infliximab, which had approximately eight years of marketing history when approved for psoriasis. FDA requested more patients -- that is 5,000 -- followed for a longer period -- that is 10 years -- for adalimumab, the most recently approved biologic for psoriasis, which had approximately five years of marketing history when approved for psoriasis in January of this year.

Issues to consider in regard to the proposed assessment of long-term safety include the adequacy of the proposed size to detect low-frequency adverse events, adequacy of the proposed duration to detect long-latency adverse events, and the adequacy of both proposed size and duration for a first-in-class new molecular entity with a carcinogenicity signal in the literature for psoriasis, a non-life-threatening condition for which numerous therapies exist.

As discussed by Dr. Yao in the briefing materials, IL-12 has been shown to have anti-tumor activity in murine tumor models, and UV-induced tumors in animal models may behave more aggressively in the absence of IL-12.

The applicant discussed the comparison that was done to the external database, specifically the SEER base. This comparison was done to assess malignancy rates in the psoriasis studies compared to

the expected rates in the general population. Standardized Incidence Ratios were evaluated using the SEER database from the National Cancer Institute.

The SEER database presents information on cancer incidence and survival in the United States, and contains information on more than 3 million malignancies. The population is based on U.S. Census data and adjusted for age, sex, and race. Non-melanoma skin cancer are not included in this database.

The Standard Incident Ratio, or SIR, is the observed number of subjects with malignancy divided by the expected number of subjects with malignancy, and if the SIR is greater than one, and observed number of subjects is greater than the expected number of subjects -- and as the applicant indicated for the placebo group, the SIR is 1.05 or 1.22 for the 45mg group and 0.17 for the 90mg group; therefore, the rates are comparable or

lower than might be expected in the general population.

Some limitations of comparison to the SEER database are that it does not permit comparison of rates of non-melanoma skin cancer to the general population, and that's because non-melanoma skin cancer are not included in the SEER database.

In databases that report rates of non-melanoma skin cancer have not been identified. These limitations may be important because the target population is possibly at heightened risk for non-melanoma skin cancer because of previous therapies, and the role of IL-12 in tumor surveillance.

In summary review of our safety data, no apparent pattern to the types of malignancies were seen through 18 months of follow-up. However, the long latency period for development of malignancies may mean that patterns would not be revealed through a follow-up period of 18 months.

The next topic is the self-administration of the product. Proposed labeling -- draft labeling proposes that, "A patient may self-inject with ustekinumab if a physician determines that that it is appropriate after proper training in subcutaneous injection technique."

Recall that maintenance dosing is proposed for every 12 weeks.

Prior to injection, the product should be inspected for discoloration and particulate matter. The product is described as being clear or light yellow in color and may contain a few white or translucent particles of protein. It should not be used if it is discolored or cloudy or if other particulate matter is present.

In the Phase 3 studies, the product was self-administered at the investigative side by the subject, under the supervision of an appropriately licensed and authorized health professional. Therefore, no subjects

self-administered outside of supervised conditions.

Concerns regarding self-administration relate to the long half-life of the product, which makes for relatively infrequent maintenance injections and prolonged immunosuppression. The relatively infrequently injections could result in possible intervals of greater than three months between follow-up visits. This could in turn result in possible delay in diagnosis and/or treatment of clinically significant conditions, some of which could result in a decision to postpone or discontinue treatment.

Because of the long interval between injections, it is unclear whether patients could become adept at adequately assessing the quality of product for injection, such as assessing for particulate matter that might preclude injection. Additionally, patients may not become adept

at injection procedures because of infrequency of treatments, and both safety and efficacy could be impacted by these concerns.

Thus, in-office visits every 12 weeks for medical assessment and a determination of appropriateness of continuation of treatment would best serve patients' well-being. The risk-benefit equation would appear to favor in-office follow-up every 12 weeks for assessment and treatment.

And the last topic, immunogenicity. The time-points of sampling in the trials allow for possible presence of ustekinumab when immunogenistic testing was done. The presence of ustekinumab could interfere with the detection of anti-ustekinumab antibodies, and could result in inconclusive antibody status due to possible assay interference.

These next two slides depict the immunogenicity testing results from the

Phase 3 trial, and they're presented by two weight categories -- less than or equal to 100kg, and greater than 100kg.

There are three categories of results: Antibody positive at any time, antibody negative, and antibody status inconclusive. And the antibody status inconclusive are those subjects who could not be classified as negative due to the possible interference from circulating ustekinumab, and excludes subjects who were antibody positive at any point.

The documented number of antibody positive subjects is relatively low in all categories; however, the number of subjects who had inconclusive status is relatively high in all categories. A similar but more pronounced pattern is seen in study T09, wherein again, relatively low numbers of documented antibody positive subjects -- and most subjects in this study had antibody status that was inconclusive.

The results revealed that antibody status is inconclusive in approximately 23 to 67 percent of subjects in study T08, and approximately 75 to 96 percent of subjects in study T09. Additionally, the results reveal a possible association between subjects heavier than 100kg and antibody positivity, and a possible association between 45mg dosing and antibody positivity.

Possible clarifying investigations of immunogenicity of ustekinumab include a clinical trial in which the testing is done at time points that have allowed for clearance of ustekinumab, or development of an assay with which the presence of ustekinumab does not interfere.

Thank you. I'd like to introduce now my colleague, Dr. Rizwan Ahmad, from the Office of Surveillance and Epidemiology.

DR. AHMAD: Good morning, everyone. My name is Rizwan, and I'm an epidemiologist in the Office of Surveillance and Epidemiology, and

I will talk about ustekinumab's safety assessment, and will attempt to guide the committee to the way forward.

I will focus on select safety concerns, challenges in assessing safety. I'll talk about sponsor's proposal, and mention some pertinent issues and questions that need to be addressed and considered in the decision-making process.

The select safety concerns are malignancies and opportunistic infections. Some of the available options to study these are Adverse Event Reporting System, or AERS, observational studies, registries, and Randomized Controlled Trials, or RCTs.

FDA's spontaneous reporting system is best suited to identify rare events with short latency. AERS may not be able to capture events with long latency such as malignancy, but may capture infections. Under-reporting and incomplete or missing information are major limitations of AERS.

In addition, we cannot calculate the incidence of an event because of lack of data on numerator and denominator, and hence, we can't quantify the risk of an event.

The conventional epi study design, such as case control and cohort, also pose challenges in assessing safety. It can take many years to accrue enough number of patients in the population. Large sample size will be needed for rare events such as malignancy. There can always be questions about unmeasured or residual confounders. Incomplete case ascertainment and under-estimation of risks because of mis-classification are some of the other limitations of observational studies.

Another option are registries, which are systematic collection of events or exposures and can be exposure-based, such as drug exposure, or disease-based, such as cancer registries.

Registries can be voluntary or

mandate free. In voluntary registry, access to drug is not contingent on being in the registry, and hence, it is less burdensome for both patients and prescribers. The limitations of voluntary registry are involuntary registries -- enrollment may pose a challenge, and those patients who enroll may not be representative of the population. Involuntary registries are usually incomplete, and capture only some of the cases and exposed persons.

In mandatory registry, since access to drug is tied to being enrolled in registry, complete information on all exposed patients and cases are captured, and this reduces selection bias. However, in mandatory registry, prescriber, patient and/or pharmacist may have to do some additional task which may make prescription sale and use of drug a little burdensome for all relevant parties.

Mandatory registry also requires

the restricted distribution of the drug. Since there may not be any incentive for patients to continue on registry after they discontinue therapy, it may be difficult to attribute the drug for events with long latency.

Another option are RCTs, or Randomized Controlled Trials, which are considered a gold standard. RCTs are primarily conducted to study efficacy of products. RCTs can also be useful for safety if adequately powered. Unfortunately, clinical trials are not normally done to answer safety questions, and that is why we have a question mark. However, if there are important safety concerns with a product prior to approval, FDA has asked sponsors in the past to conduct RCTs to study relevant safety issues.

Randomization eliminates selection bias and provides a comparator group. RCTs are more likely to capture events of

interest, and have a greater ability to evaluate some safety signals.

As I said earlier, RCTs are typically done for efficacy assessment, but they can be conducted to clarify certain safety issues. But RCTs when done for efficacy assessment may have certain limitations. The number is low, focus is narrow, scope is limited, duration is short, and generalizability is limited because of exclusion of patients with serious diseases or comorbidities and concomitant medications.

Now let me talk about the sponsor's proposal. The sponsor plans to conduct a registry, PSOLAR, which is the same as in place for infliximab, another of their product, which had eight years of marketing history. The primary objective is to evaluate the safety of ustekinumab in patients with chronic moderate to severe plaque psoriasis. There are also some secondary objectives.

The design of the PSOLAR -- as I said, it's a registry. The sponsor's plan is to recruit patients from North America, Europe and Asia. The enrollment period is two years, and the observation period for each patient is eight years, and the total duration of the registry is 10 years.

These are the inclusion criteria: adult patients 18 years or older with psoriasis, patients who can receive or are on conventional systemic agents or biological therapy.

The sample size of the registry will include 4,000 ustekinumab-exposed patients and 4,000 other patients exposed to conventional agents or biologics with whom comparison will be made.

According to the protocol, the sponsor will attempt to capture all serious adverse events, and data will be collected at baseline and at six-month interval. Data includes demographics, medical and family

history, previous treatments, history of concomitant medications, health, economic and quality of life indicators.

Interim analysis which will include descriptive data will be submitted to the FDA annually. The protocol doesn't include any statistical analysis plan.

Limitations of PSOLAR as designed. Patient recruitment may be a challenge. Adverse events with long latency such as malignancy may be difficult to capture. In general, it takes a long time between exposure and clinically apparent cancer. Rare events may be outside power range. Follow-up and case ascertainment may be difficult.

Assessing dose and duration of therapy may be difficult as well. The registry doesn't address patients who will switch therapies.

Sponsor plans to recruit about 40 percent of patients from outside North

American, including 20 percent, or 800, from Asia. We know that the background rate of malignancies and infections are different in Asia compared to North America, and also, psoriasis in Asian population is different from North America.

Patients may not be representative of the general population. And the logistics of following patients longitudinally and tracking their health outcomes are difficult.

Registry size and power calculation. Power is low, about 60 percent for rare adverse events of .01 percent, or with an incidence of 1 in 10,000 according to the assumptions made by the sponsor. For example, according to information derived from the Centers for Disease Control and Prevention website and U.S. Census data, the background rate of non-Hodgkin's lymphoma in people 15 to 49 years is about 8 per 100,000, and this is far lower than the .01 percent cited by the sponsor.

If the background rate of an adverse event is .5 percent, or 1 in 200, the registry size has enough power -- and we know that the outcome of greatest concern, that is malignancy, has a far lower background than .5 percent. In other words, the sponsor's proposed registry as currently designed is far too small, and doesn't have the power to identify events of interest even if a substantial increase in risk exists.

There are certain pertinent issues that need to be considered when making a risk-benefit assessment of ustekinumab. We need to be aware that ustekinumab is a new molecular entity, first in its class, with no prior marketing history, unlike some other biologics already approved for psoriasis.

The total number of patients exposed to ustekinumab for psoriasis in clinical trials is about 2,200, and the maximum duration of exposure has been for about 76 weeks or 18 months, involving under

400 patients.

There is a potential signal for malignancy for ustekinumab based on the literature as alluded to by previous speakers, and this is unlike other biologics. And as mentioned by Dr. Brenda Carr, psoriasis is a non life-threatening disease for which alternative therapies exist.

Now let me come to questions that need to be addressed within the context of the previous issues, which are: what is the risk of malignancy or opportunistic infections after treatment with ustekinumab?

The answer to this question is that we have inadequate safety data to clarify significant safety concerns associated with this biologic, so the question is, should ustekinumab be approved when there is sparse safety data, and alternative therapies exist for the treatment of psoriasis?

The next question is, when and what other strategies can be undertaken to assess

the risk of treatment with ustekinumab? The options before approval are to conduct much larger and longer-term clinical trials to build the safety database, like it was done in the case of some already approved biologics for psoriasis.

I have already discussed some of the options after approval, and some are listed in the questions that we have asked you, but the question is, do we need to take this route in the age of safety first and (inaudible) environment? And this is what you as a committee have to advise us. Thank you.

And finally, I would like to thank all these individuals who helped me in this talk.

DR. BIGBY: I'm aware that there are questions from Dr. Ringel and Dr. Shwayder to the sponsor, but at this point I think we'll take clarifying questions for the agency, and I promise I'll leave time

before we break for lunch for the other questions to be asked.

Rob and then Mary.

DR. STERN: I have two unrelated questions. The first is, at least in my experience, many patients require even lower doses of a systemic therapy to maintain their psoriasis in good extent, and one always has to look at duration and dose. The trials have only looked at constant dose, and essentially with the withdrawal, what the duration where one begins to see flares.

Is there any thoughts of in fact requiring or doing trials that would demonstrate whether or not lower maintenance doses than that were required were efficacious for clearing might be required.

You know, if you look at the TNF-alpha inhibitor, there is a difference in the first 12 weeks versus maintenance recommendations in psoriasis. And I think if you look at how many of us have used

methotrexate for 30 years, there's a difference in clearing dose and maintenance dose, and duration is not quite as flexible, which the pharmacokinetics would suggest.

So my question is, is there any thought to looking at whether in fact lower exposures, post-clearing, post-12 weeks, might be as effective and presumably safer for long-term maintenance for this chronic disease?

And then I have a second unrelated question.

DR. WALKER: I can answer that. I think that's one of the questions we're posing to the committee. Obviously, the elements of dose ranging are important, and your comments on establishing the dose duration and frequency and what the agency should be looking for in clinical trials is of interest to us.

We have no specific data for this product, I believe, in some of these areas.

DR. STERN: So we'll be a little bit

blind in terms of really what's likely to be the long-term exposure, what's the optimal dose for maintenance of clearing?

DR. WALKER: I believe we have the data that has been presented today, and any considerations beyond that, we would be looking for the advice of the committee.

DR. STERN: My second question has to do with CRO-managed registries. The first biologic was approved for psoriasis nearly six years ago -- I think the fall of 2002. And I'd like to ask the FDA what new substantial safety information for any of the drugs that have been approved for psoriasis in these six years has come from those, and to compare it -- in terms of long-term safety -- and to compare the findings from these with -- for example, the Bonnett's paper which was relatively short-term in terms of a meta analysis of a clinical trial data -- so have we shown efficacy over the last 5-3/4 years in terms of new robust safety information?

DR. AVIGAN: I'll just make some general statements. I think your question is well-placed, and that we don't yet have a sufficient experience to conclude that observational studies that we set into motion with the sponsors running them have provided us with useful new signals, but it's still something that we need to explore further and work through. And one of the questions that is being posed to the committee is asking their advice about the utility of this kind of approach.

Having said that, the logic of doing these studies is to look not only for very rare events, which they may not be powered to do, but also to look at a general clinical experience about other kinds of adverse events in this arena of biologics, which are more common and which give us concern -- specifically infections and also atypical infections, which are not all that rare for some of the agents that have been

used -- and not only learning what are the new signals, but learning about what are the situations, the clinical scenarios, in which these occur.

DR. BIGBY: Dr. Drake?

DR. DRAKE: My question was -- Rob beat me to it. I think I was the acting chair of the first biologic approval -- committee that recommended approval, and it seemed to me that we certainly requested follow-up data on things such as carcinogenicity -- and this is five years out. Do you have -- I want to just follow-up on Rob's question. Has anybody reported out anything, and are you expecting anybody to report out anything in terms of these follow-up recommendations from the sponsors?

DR. AVIGAN: Again, we do expect the sponsors to report to us on their experience. One of the road blocks from just implementing these studies is the enrollment step, that these studies which have been proposed -- roughly in the order of enrolling 4,000 or 5,000 patients

per treatment group -- has been that to some extent, that's a kind of compromised number based upon what is doable and what would be sufficient to get some empiric experience.

But the road block has actually been in the enrollment step; that is, it has been difficult for some of the sponsors to find -- to ramp up quickly patient enrollments to get a sense of what actually is going on. And I think one of the learning experiences that we've had in the last few years is that despite the fact that these studies have been proposed and planned for, they have not been robustly implemented. And so that's, I think, where we are as a general theme with many of these studies.

Having said that, some of the cancer signals that we have seen have come from other sources of information such as the Adverse Event Reporting System, where we see rare signals that are sometimes very impressive. A recent example is the

hepatosplenic T-cell lymphoma signal that was appreciated from the AERS database in patients with Crohn's disease, primarily pediatric patients -- a very compelling adverse event signal, safety issue that got into the label, as well as in clinical trial meta-analyses where there was randomized datasets that were available in some cases, and have led to labeling for some of these products.

So it really ends up being a kind of pastiche of different data streams that come together that together give us a sense of malignancy risk, where in some cases we're looking at very low background rate malignancies, where we see a cluster of events which are compelling because the background rates are so low -- and in other cases where the background rates of some other kinds of malignancies are higher, and where the methodologic challenges require perhaps a different approach, such as

randomized datasets.

DR. DRAKE: Thank you.

DR. WALKER: I think we have another comment --

DR. DRAKE: Please do. Yeah.

DR. WALKER: From FDA.

DR. DRAKE: I'd like another comment.

MR. SIEGEL: Hi. I'm Jeffrey Siegel. I'm in the division of anesthesia and rheumatology products. I've been involved in overseeing development of the biologics for rheumatoid arthritis and other rheumatic diseases. The question as I understand it is what's been the usefulness of registries in assessing safety events, and I think it's a very good question.

The short answer in my experience is that registries have not been that useful for detecting new safety signals. Most of the safety signals that we've gotten, the TB signal, malignancy signals, demyelization, and so on, have come from either spontaneous

post-marketing adverse reports or from clinical trial data. But the registries have really been essential for us -- when we get a signal -- to try to bracket what the level of concern is. So for example, when we got signals about a malignancy risk, there were registries in Sweden and other countries in Europe that showed that the risk of malignancy was no higher in people receiving TNF blockers than in people receiving other products for rheumatoid arthritis.

So that was one very useful function of the registries.

DR. STERN: But those weren't registries that came from FDA in agreement with the sponsors. Those are very different kinds of registries. I was specific in terms of -- SOCOR is very much like the last five proposals, what we've gotten from those after 5-3/4 years. I understand the utility of the cancer registries in Scandinavian countries and other places, which are very good for pharmacoepidemiological

research, but my question was more specific.

MR. SEIGEL: I can just make one quick comment on that. So the reason that European registries are particularly helpful is because they're comprehensive -- all patients receiving biologics in those countries -- and because they're linked to malignancy databases. Nonetheless, for each of these signals that we detected from another way, we always look at the FDA-required registries to see what the level of signal is in those populations, and it is helpful, but perhaps not as definitive as other sources.

DR. BIGBY: We're going to go on. I just want to sort of caution the table. This is not part of the discussion, it's just clarification, and we can have this kind of weighing of the answers in the afternoon.

Eileen?

DR. DRAKE: I had a follow-up -- I had a two-part question. I wanted to ask Dr. Yao on his slide on number three, your third slide,

where it talked about the non-clinical evaluation for small molecules versus biologics, and under carcinogenicity, it said that the biologics are historically not provided, and I wondered why is that?

DR. YAO: Based on ICH is (inaudible) for that guidance for the biological, they generally don't recommend -- guidance don't recommend for the carcinogenicity studied, unless there's some concern, so for those biological approved for the psoriasis, there's no carcinogenesis contacted by the sponsor --

DR. DRAKE: But that's still not -- I mean, I understand that's the policy and that's what you do, but I remember one of these gave a signal for a potential B-cell lymphoma on down the road, and I guess I don't understand why it's not part of the requirement.

DR. YAO: Another reason is that for the biological, typically we cannot use the drug product in the animal, because we have to develop analogue in the mice or rat. We need

another analogue. That means we need to develop another product to test the information regarding the other information so that we can do a two-year carcinogenic study.

DR. BIGBY: Dr. Ringel?

DR. RINGEL: Thanks. Many questions have been answered by the FDA, and I appreciate that. I'm going to limit this simply to questions not discussion. First of all, has the FDA done an analysis that's stratified the PASI 75 data on the basis of disease severity? Have you looked at the data in that way?

DR. SHWAYDER: The malignancy data?

DR. RINGEL: No. Just PASI 75 versus disease severity. That's what I'm interested in.

DR. FRITSCH: I think we have looked at some of those analyses. I don't have the results at my fingertip, but that's part of the comprehensive analyses that we will be done.

DR. RINGEL: That's something I'll probably ask the sponsor later on then.

DR. BIGBY: Hold on, Eileen. You can ask them now because -- I mean, you could ask them now.

DR. RINGEL: Does anyone have that data for me?

DR. GUZZO: I did show the data in my presentation. If we can go back to the subgroup analyses, please, in my main presentation. And we did look at PASI 75 response by disease severity. Slide up, please. And you can see it broken down at both doses. PASI 75, 45 and 90, cutting the data at PASI by less than 20 and greater than or equal to 20, PGA less than 4, greater than or equal to 4, and then baseline body surface area by less than 20 and greater than or equal to 20.

And generally we see a consistent response across all those, so it works as well for moderate psoriasis as it does for severe psoriasis using those arbitrary cut points.

DR. RINGEL: Second question, what are

the exclusion criteria for entry into this study? For example -- I really haven't read that anywhere in the data we've been given.

DR. GUZZO: Do you want me to answer that?

DR. RINGEL: In a moment. I have two specific -- we don't know how the drug is metabolized, so I'm specifically interested in patients with any degree of liver disease or any degree of renal disease were included. I'm interested, because so many patients are obese and steatohepatitis, fatty liver, with elevated liver enzymes, with diabetes, if they had borderline renal function, were any of those patients excluded, or was any of that tested before they entered the study?

Patients -- there was an exclusion criteria for creatinine above 1.5, patients had to -- any patient who had liver function tests above 1.5 times the upper limit of normal. Generally, antibodies are metabolized through the same pathway at which

natural antibodies are thought to be metabolized. They're not metabolized through the p450 system so you don't have to worry about issues of drug interaction, but generally thought to be metabolized in the same way as natural antibodies.

The last question is probably obvious, but I'm going to ask it anyway. Were all patients who were lost to follow-up treated as treatment failures?

DR. GUZZO: So at week 12, there was an ITT analysis, and all patients are accounted for. After week 12 -- can I have 535, please -- so after week 12, we analyzed the data by all observed data. So that means that -- but we also applied treatment failure roles. So anybody who used a prohibitive concomitant medication or had inadequate response to treatment, was treated as a treatment failure. Additionally, we follow all patients who stop study for adverse events for 20 weeks, so we obtain their efficacy data and they're included

in the analysis.

If you do -- can I have the slide up, please? If you do an intent to treat analysis -- the missing data is small, first of all -- and you can see the numbers at the bottom of the page, where you start out with 255 and then 246, 256 in the 90mg down to 238. So this was the pre-specified analysis, and if you use last observation carried forward and you do an intent to treat analysis, you see similar responses.

DR. RINGEL: So all incomplete responders, all lost to follow-up, everyone was considered a treatment failure; is that correct? At 40 weeks.

DR. GUZZO: Not everybody who was lost to follow-up was considered a treatment failure. They're not included in the analysis, but if they were a treatment failure by our predefined treatment roles -- in other words, they stopped treatment because of an inadequate response or they used a prohibited concomitant medication,

they're included in the analysis as treatment failures.

DR. RINGEL: Thank you.

DR. BIGBY: Dr. Thiers?

DR. THIERS: I'd like to speak to the remark made by more than one of the presenters, and I'll quote it so I don't get it wrong. "Psoriasis is a non-life-threatening disease for which alternative therapies exist."

It may be a skin disease, but I would urge the panel and everyone in attendance not to trivialize it. I mean, psoriasis has a huge impact on patient lives, and as I think Dr. Lebwohl mentioned, even minimal involvement could basically render somebody unemployable.

And in terms of alternative therapies, there are alternative therapies out there, but looking at the data, probably the only one that comes close in terms of efficacy is infliximab, which has to be given intravenously, and cyclosporine, which is a

non-biological which has huge safety concerns.

Now, I certainly share the concerns of probably everybody here in terms of what the long-term safety of this drug is, but I think as with any drug, we have to weigh the risks against the potential benefits. And my question to the FDA presenters, whoever cares to answer would be, somebody mentioned the possibility of doing more clinical trials. What kind of clinical trial would address these long-term latency questions?

Are you talking about a trial that would be 8 or 10 years in duration? And are you talking about a trial that would be pre-marketing or post-marketing?

DR. WALKER: I'll address that. I share your concerns. I believe that what we're trying to do today is put the options on the table for the committee to discuss. There's certainly no intention to trivialize psoriasis. It's a very serious condition and it