FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEETING (DODAC)

Silver Spring, Maryland

Tuesday, June 17, 2008

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P R O C E E D I N G S

(8:00 a.m.)

MS. WAPLES: If everyone could take their seats, we're about to begin.

Good morning. I would first like to remind everyone present to please silence your cell phones if you have not done so already.

Ms. Rita Chappelle is the FDA press contact. Please direct all inquiries to Ms. Chappelle.

DR. BIGBY: Hi. Good morning. I'm Dr. Michael Bigby. For topics such as those being discussed today at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for a discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the

record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

I would now like to go around and have the members of the committee introduce themselves, starting on my far right.

DR. STRAHLMAN: Dr. Ellen Strahlman, industry representative.

DR. SHWAYDER: Tor Shwayder, pediatric

dermatology, Henry Ford Hospital.

DR. RINGEL: Eileen Ringel, dermatologist, Maine.

DR. HECKBERT: Susan Heckbert, general internist and epidemiologist, University of Washington.

DR. DRAKE: Lynn Drake, dermatologist, Harvard Medical School, Massachusetts General Hospital.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois, Chicago College of Pharmacy.

DR. LEVIN: Art Levin, Center for Medical Consumers in New York.

DR. BIGBY: I'm Michael Bigby, Department of Dermatology, Harvard Medical School, and Beth Israel Deaconess Medical Center.

DR. MAJUMDER: I'm Mary Majumder. I'm at the Center for Medical Ethics at Baylor College of Medicine, and I'm the consumer representative.

DR. STERN: I'm Robert Stern. I'm at Harvard Medical School in the Beth Israel Deaconess Medical Center, and a dermatologist.

DR. KATZ: Robert Katz. Private practice, dermatology, Rockville, Maryland.

DR. CARR: I'm Brenda Carr. I'm a medical officer with the FDA in the Division of Dermatology and Dental Products.

DR. IYASU: I'm Sol Iyasu. I'm the director of the Division of Epidemiology, Office of Surveillance, FDA.

DR. AVIGAN: Hi, I'm Mark Avigan, director Adverse Events Division and the officer (inaudible) Epidemiology.

DR. WALKER: Good morning, I'm Susan Walker, director of the Division of Dermatology and Dental Products at the Food and Drug Administration.

DR. BEITZ: I'm Julie Beitz, director of Office of Drug Evaluation Three in CDER.

MS. WAPLES: The Food and Drug Administration (FDA) has convened today's

meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee or special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC

Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for particular individual services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion at today's meeting, members and temporary voting members of this committee who are SGEs have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the committee will discuss and make recommendations regarding, BLA, 125261 CNTO 1275, Ustekinumab. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by the committee, members and temporary voting members, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ellen Strahlman is participating in this meeting as a non-voting industry representative acting on behalf of

regulated industry.

Dr. Strahlman's role on this committee is to present industry interests in general and not any one particular company. Dr. Strahlman is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. WALKER: Good morning. First, I would like to welcome everyone to our meeting today, both the participants and the observers. I'd like to sincerely thank the committee

members and the assembled consultants, members from the Dermatologic and Ophthalmic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committees. We really appreciate your willingness to take this time from your busy schedules to participate in this meeting.

Today, we're going to ask you to provide discussion and advice concerning the safety and advocacy of ustekinumab, a biologic therapy proposed for use in the treatment of adult patients with plaque psoriasis. Ustekinumab is a new molecular entity that represents a new class of therapy with a new mechanism of action. This product is not currently approved for use in the U.S. or any other country.

Plaque psoriasis is a chronic, relapsing disease characterized by variable chronic features. Most studies indicate that once psoriasis appears as an early localized disease, it persists throughout life,

manifesting at unpredictable intervals. Although spontaneous remissions can occur with varying frequency, it generally representing a lifelong burden for affected patients.

You've received the summary information from the sponsor and from FDA, and our interest today is for the committee to focus discussions on the benefit/risk assessment for use of this new molecular entity in otherwise healthy patients with plaque psoriasis.

The patients proposed for treatment are those with cutaneous disease, and the sponsor is not at this time asking approval for patients with psoriatic arthritis.

Considering the benefits of ustekinumab, we'll ask you to consider the outcomes demonstrated by the clinical trials that you'll hear about today. We'll also ask you to discuss the proposed dosing strategies.

In considering the risks of ustekinumab, we'll ask you to consider the novel mechanism of action, and implications if any for carcinogenesis in patients.

Sponsors seeking approval must provide from the clinical trials a body of evidence that adequately characterizes the product safety profile.

We'll ask you to discuss the sufficiency of the safety data to support approval, and to discuss whether the numbers of subjects studied in the clinical trials and the duration of these studies is sufficient to adequately inform the safety of ustekinumab for the treatment of plaque psoriasis in adults.

And finally, we'll ask you to provide discussion and recommendations on the sponsor's risk assessment proposals.

DR. BIGBY: I'd just like to have you all look at the list of questions to see that there are many that we have to discuss,

and so it would be very helpful for both the sponsors and the FDA to be brief and succinct in their presentation, and any extra minutes you don't use will be greatly appreciated.

So I'd like to introduce the first presenter from the FDA, Laurie Graham.

DR. GRAHAM: We're done. Thank you. So good morning everybody.

My name is Laurie Graham. I'm in the Division of Monoclonal Antibodies in the Office of Biotechnology Products. I'm the primary product quality reviewer for ustekinumab, also known as CNTO 1275.

Today, I'm going to be talking in general about biologics and monoclonal antibodies, and then specifically about ustekinumab and its mechanism of action.

So biologics and small molecule drugs differ in some important characteristics. The first and most striking is relative size. Shown in the figure here is the Fab fragment of a monoclonal antibody

compared to a statin. The Fab fragment is the region of the antibody that binds to the target.

The Fab fragment represents about 1/3 of a monoclonal antibody, so the molecular weight of the Fab fragment is about 50,000 Daltons (Da). So an entire monoclonal antibody has a molecular weight of about 150,000 Da. This is in comparison to a statin, which has a molecular weight of only 400 Da.

This increased size of biologics generally means that biologics have an increased complexity. For example, there can be post-translational modifications which can result in heterogeneity of the final drug product.

Biologics are derived from cell substrates, so you're always concerned about impurities such as adventitious agents. Biologics are required to have a potency assay which reflects its mechanism of action,

and its potency assay is utilized during release of the final product.

And finally, biologics can illicit immunogenicity in patients, and this immunogenicity is reflected by anti-product antibodies in the patient's serum. And sometimes these anti-product antibodies can neutralize the activity of the product.

So now I'm going to switch gears and talk specifically about ustekinumab and its mechanism of action.

Ustekinumab is a fully human IgG1 kappa monoclonal antibody. It was developed in a transgenic strain of mice in which the mouse immunoglobulin genes have been inactivated and replaced with the human immunoglobulin genes. Using DNA recombinant technology, the antibody is produced in a well-characterized cell line using standard bio-processing technology.

Ustekinumab is specific for the p40 subunit of the IL-12 and IL-23 cytokines. By

binding to p40, ustekinumab inhibits the ability of IL-12 and IL-23 to bind to their cell surface receptors. In this manner, ustekinumab inhibits both IL-12 and IL-23 signaling.

So next, I just want to briefly review IL-12, IL-23 and their signaling.

Both IL-12 and IL-23 are composed of two subunits. As I've indicated previously, they both utilize the p40 subunit, and then they each have a unique subunit -- p35 for IL-12, and p19 for IL-23. In addition to sharing p40, these cytokines also share a receptor chain, the IL-12-beta one receptor chain, and then they each have a unique receptor chain.

IL-12 signals through the JAK2 and TYK2 kinases, and the STAT4 transcription factor. Downstream of IL-12 signaling there's a production of interferon gamma by natural killer and key cells, and a differentiation of naïve T-cells into TH1

cells. These TH1 cells then produce a host of cytokines. This in turn inhibits another subset of T-cells, T Helper 2 cells. These immediate effects of IL-12 signaling mean that IL-12 plays a role in host defense, and this includes tumor surveillance.

Like IL-12, IL-23 signals through the JAK2 and TYK2 kinases; however there is evidence that IL23 signaling utilizes different transcription factors. For example, IL-23 seems to utilize STAT3 predominantly instead of STAT4, and there's some evidence for a unique transcription factor, RR-gamma-T. Downstream of IL-23 signaling is the survival and proliferation of a new subset of T-cells, Th17 cells.

Like IL-12, IL-23 plays a role in host defense, but there's a growing body of evidence that IL-23 and Th17 cells mediate autoimmune diseases such as psoriasis.

So as I've said, ustekinumab is able to target both IL-12 and IL-23. Its

ability to target two different cytokines makes it somewhat unique.

When p40 was initially discovered, it was only known to be a component of IL-12, and p40 was found to be upregulated in psoriasis plaques. This led to a paradigm in which IL-12 was considered to be a key cytokine mediating psoriasis. It was during this period of time that ustekinumab was developed. Subsequently, it was discovered that IL-23 also uses p40.

If you look in psoriasis plaques for the unique subunits of these cytokines, you find up-regulation of p19, but not p35, so all of this has led to a major shift in the paradigm regarding psoriasis from IL-12 as the key cytokine to IL-23. So while the rest of my talk is going to be dealing with the current IL-23 paradigm of psoriasis, I do want to point out that a role for IL-12 has not been ruled out.

So during psoriasis, there's a

possible initiating event such as trauma or infection. This event leads to an activation of cells of the innate immune system. This includes professional antigen presenting cells. These innate immune cells then produce a host of soluble factors and cytokines, some of which are shown here. The cytokines include TNF-alpha IL-6, IL-1, and IL-23. When a naive T-cell is activated by an antigen-presenting cell in the presence of IL-23, IL-6, and IL-1, there will be the differentiation survival and proliferation of Th17 cells. These Th17 cells produce a subset of cytokines, some of which are shown here.

These include TNF(alpha), IL-17, IL-21, and IL-22. The result is keratinocyte stimulation, proliferation and chemokine production. I've highlighted IL-22 here because IL-22 has been shown to inhibit the terminal differentiation of keratinocytes, which is a key event during psoriasis.

As a result of keratinocyte stimulation and chemokine production, there is an infiltration of innate immune cells and infiltration of T-cells into the skin to the site of inflammation. And I want to point out that I have described this in a very simplistic fashion, but all of these different cellular compartments, cytokines, and chemokines are interacting with each other to enhance each other's activation and to enhance the immune and inflammation of the skin.

And in conclusion, I want to fit the currently improved biologics and ustekinumab into the psoriasis network. So there are currently five approved biologics for psoriasis. Amevive and Raptiva target receptors on T-cells. Amevive targets the CD2 receptor, and Raptiva targets LFA-1. These are general T-cell immunosuppressive agents. Remicade, Enbrel, and Humira are all TNF-alpha blockers. TNF-alpha has been shown

to be an important stimulator of keratinocytes, and TNF-alpha is not only produced by T-cells, but it's also produced by cells of the innate immune system.

And finally, ustekinumab targets both IL-23 and IL-12. By targeting IL-23, ustekinumab is expected to inhibit the production of Th17 cells, the T-cell subset which appears to mediate psoriasis. It's ability to specifically target this T-cell subpopulation makes it mechanism action somewhat unique.

Thank you very much for your attention.

DR. BIGBY: So I now open the floor for the industry presentations.

DR. JONES: Thank you. Mr. Chairman, members of the advisory committee and the FDA, good morning. My name is Stella Jones and I'm head of Centocor's Regulatory Affairs Department. At Centocor, our research is focused on targeted biologic therapies to treat

disease with (inaudible).

On behalf of Centocor and Johnson & Johnson, I would like to express our appreciation to the FDA for this opportunity to present before the advisory committee information on ustekinumab.

Ustekinumab is a fully human anti-interleukin 12/23 monoclonal antibody, with a molecular weight of 148,600 Daltons. Its proposed trademark is STELARA. It is also known as CNTO 1275, originated from Centocor's discovery laboratories.

I would like to begin Centocor's presentation by briefly reviewing the regulatory history of ustekinumab's development for the treatment of plaque psoriasis, starting from the identification of interleukin-12 nearly 20 years ago. The cytokine interleukin-12 was first identified in late 1988 and published in 1989 in the Kobayashi paper. Georgio Trinchieri led the team that identified this cytokine at the

Wistar Institute. They first called interleukin-12 by the name natural killer cell stimulatory factor. A second group of researchers independently identified the same cytokine, but named it cytotoxic lymposine maturation factor.

By 1990, the complete sequence was known and it was designated interleukin-12. After IL-12 was identified, sequenced, and cloned, Centocor commenced the development of an anti-IL-12 monoclonal antibody that targets the p40 subunit.

In 1992, human antibody transgenic mice were developed. This technology was used to generate fully human antibodies. In the year 2000, Centocor submitted an IND to the FDA to investigate the therapeutic potential of ustekinumab in psoriasis. As Laurie indicated earlier, at the same time interleukin-23 was identified by DNAX scientists. They discovered a new protein p19 forms a complex with the p40 subunit

IL-12 to form IL-23 protein. Therefore, IL-12 and IL-23 shares a common p40 subunit and p40 antibodies -- such as ustekinumab binds both to IL-12 and IL-23. As shown in this timeline, Centocor initiated its Phase 1 trials in 2001, followed by a Phase 2 dose range study in 2003. An end of Phase 2 meeting was held with the FDA in May 2005, after which, Centocor initiated its Phase 3 program.

A pre-BLA meeting was conducted with the FDA in March 2007, leading to the first biologics license application of an anti-IL-12/23 monoclonal antibody to the FDA in November 2007.

I was going to describe next the mechanism action. Since Laurie has presented very thoroughly -- and as the chairman indicated, I want to be brief, so if you can show through the end of this slide, the only thing I would like to point out is that in contrast to some other antibody therapeutic,

ustekinumab is not a depleting antibody, and it does not induce lymphocyte depletion as its mechanism of action. Later in our presentation, Dr. Newman Yeilding will describe data on the immune function of patients treated with ustekinumab.

I would like to transition from the mechanism of action to the actual affect in patients. This is one of the first patients with plaque psoriasis that treated with ustekinumab. Sixteen weeks after administration, we observed a significant reduction of psoriatic plaques. Results like this, combined with a lack of early safety signals, that encouraged us to advance this molecule to Phase 2 and Phase 3 investigation in plaque psoriasis.

A skin biopsy obtained from a Phase 2 psoriasis patient reveals the effect of ustekinumab at the microscopic level. On the left, in the pre-treatment biopsy, one can see the psoriatic legions are

characterized histologically by epidermal hyperplasia and infiltrating T-cells. Following treatment with ustekinumab, the histology shows normalization of the epidermis and a reduction in T-cell. Notably, T-cells were not depleted, but reduced to numbers approaching that found in normal skin. Again, later, we will describe the data on T-cell function of psoriasis patients treated with ustekinumab.

In order to support the regulatory approval of ustekinumab in psoriasis, Centocor designed and conducted a comprehensive development program to establish efficacy and characterize the safety profile. The development program includes two Phase 1 studies, one dose range Phase 2 study, and two large Phase 3 trials. Both Phase 3 trials have incorporated five-year extensions to capture long-term safety and efficacy in psoriasis patients treated with this product.

Additionally, safety data from studies conducted in three other indications, namely multiple sclerosis, Crohn's disease, and psoriatic arthritis, were also submitted to the FDA. These studies included patients on concomitant immunosuppressant as well as higher doses than those tested in the psoriasis program, and therefore provide a broader scope of safety assessment.

The comprehensive clinical program in patients with psoriasis have provided substantial evidence of effectiveness of ustekinumab in the proposed indication, with a well-characterized safety profile comprised of 3,800-plus patients, of which over 3,300 patients received ustekinumab. It is important to note that over 1,200 patients were treated with ustekinumab for at least one year, providing a relatively large database to characterize the long-term safety profile of ustekinumab.

We have with us several experts who

can help address questions the advisory committee may have. They are Dr. Jeffrey Anderson, professor of internal medicine cardiology at University of Utah; Dr. Alexa Kimball, vice chair of dermatology at Massachusetts General Hospital; Dr. James Kreuger, professor and senior physician, medical director of investigative dermatology at the Rockefeller University; Dr. Mark Lebwohl, chairman of dermatology at the Mt. Sinai School of Medicine; Dr. Robert Schreiber, alumni endowed professor, pathology and immunology, at Washington University School of Medicine; Dr. William Schwieterman of Tekgenics; and Dr. Jonathan Wilkin of Wilkin Consulting.

We hope you will find all our experts' extensive knowledge and experience valuable.

Finally, I will conclude with an overview of Centocor's presentation. First, Dr. Kimball will present the clinical

background of moderate to severe plaque psoriasis. Then, Dr. Cynthia Guzzo, a dermatologist from Centocor's clinical R&D team, will review efficacy of ustekinumab.

Dr. Newman Yeilding, also a member of Centocor's clinical R&D team, will discuss safety of ustekinumab. After which, Dr. Peter Callegari of Centocor Medical Affairs will present the risk management plan.

And finally, to conclude, Dr. Mark Lebwohl will review the unmet medical need in systemic psoriasis treatment.

Now, it is my pleasure to introduce Dr. Kimball.

DR. KIMBALL: Thank you so much for allowing me here today to talk about both the incredible progress we've made in understanding and treating the chronic skin disease psoriasis, but also I want to talk to you about areas where we still need real and meaningful improvements in the care of what I consider an at-risk population.

I don't think it's a surprise to anyone who works with this disease that it is a debilitating illness with substantial morbidity, but patients with psoriasis become quite expert at actually hiding their disease and their suffering, and so I think the magnitude of what they experience and their distress is sometimes overlooked.

As you can see from these pictures, this is a disease that can involve any and all parts of the body in real and potentially incapacitating ways.

Psoriasis affects approximately 2 to 3 percent of the population worldwide, and nearly one quarter of patients have what we would call moderate to severe disease. What we've also learned in the past ten years is not only a better understanding of the biology behind this immune derangement, but we've been able to quantify for the first time the additional health dimensions it can affect. Its impact is broad, and includes

decreased physical and mental well-being, economic consequence, and multiple comorbidities, of which psoriatic arthritis is probably the best known and affects up to 30 percent of patients, but also importantly, depression, obesity, diabetes, hypertension, and cardiovascular disease.

This seminal work by Rapp et al., reported about a decade ago, was a real wake-up call for us. It demonstrated quite clearly that the impact of psoriasis on physical health compared to other diseases using the standardized quality of life measure, the SF-36, was profound, and that the decrement was substantially similar to other diseases such as arthritis, diabetes, and lung disease.

Perhaps not as surprising, but I think still dramatic, was their finding about the profound impact of psoriasis on mental health, and you can see that here compared to other diseases and to depression itself.

We are just at the beginning of understanding and beginning to quantify the economic impact of psoriasis, and early studies are demonstrating what we've suspected all along. Psoriasis is associated with an increased number of sick days and causes financial distress for people who live with it.

In a study that I did at the National Institutes of Health in people with moderate disease, we found that 23 percent of patients said psoriasis affected their choice of career. You can imagine that if you're in sales or any other job where you're in touch with the public, that being perceived as if you have a contagious disease, which is a common experience of our patients, can be devastating.

Other studies have shown a high level of financial distress because of psoriasis, a negative impact on work productivity, job retention, and missed work

days.

In one study of severe psoriasis patients, over half were not working or retired, and a full 34 percent of the non-working patients attributed their inability to hold a job because of their psoriasis, and employed patients missed a mean of 26 days of work a year because of their disease.

Now, in the past few years in particular, we have also come a long way in understanding that psoriasis is a systemic disease characterized by an increased risk for multiple comorbidities. Psoriasis patients are at risk for obesity, diabetes, hypertension, heart failure, myocardial infarction, and lymphoma. Some of these seem to be related to the underlying inflammatory nature of the disease, and others to the socio-behavioral factors such as obesity and alcohol misuse that seem to be part of the emotional toll that psoriasis takes.

Indeed, approximately half of psoriasis patients have feelings of anxiety, depression, and anger -- and I think many of us were really stunned to find that 5 to 10 percent of psoriasis patients report suicidal ideation at some point because of their skin.

Quite recently, Joel Gelfand and his colleagues added yet another dimension to this story by showing that patients who had a severity that warranted treatment with light or other systemic therapy have a decreased life expectancy by several years, even after adjusting for risk factors such as obesity.

All of this data reinforces strongly that this is a disease that needs to be treated aggressively in some people, and in my view, early, in order to prevent some of these longer-term sequelae from developing.

So that brings us back to therapy. This is a picture that I took several years ago after asking one of my patients to bring

in the contents of his medicine cabinet, and I think it's a powerful representation of what people with psoriasis historically have had to go through to keep their disease under control. It's a miserable, time-consuming, confusing, messy, and I think inadequate experience. Now, the good news for patients in general is that we've come a long way in recent times, and our treatment approach has subsequently evolved.

Our traditional treatment paradigm used a stepwise approach, starting with topicals, moving towards phototherapy, and then if that failed, progressing to systemic agents. Now I think that most of us who treat a spectrum of patients that range from mild to severe divide them really into two categories, those with localized disease that's amenable to topical treatment, and those with moderate to severe disease who merit more aggressive treatment and simply cannot be maintained on topicals alone.

The decisions for these patients who are candidates for systemic therapy have become I think more holistic and are guided by the patient's needs, including their disease severity, their employment, their underlying health status, and their economic and social needs as well.

I really consider all three modalities that you see here at the beginning -- light, traditional systemic agents, and biologics -- and then work through with the patient what will be most effective, safest, and most appropriate for them given all of the other considerations, and including the recognition that I may be treating them for decades to come.

It does make for some very long office visits these days. But even with all the options that I have available to me now, I still run into a number of limitations as I walk through these therapeutic discussions with my patients. Many are frustrated by the

lack of efficacy, and even more so by the loss of response that we sometimes see. Some are obese and may not respond well to standard dosing, and others have comorbidities that preclude certain approaches, especially with the known toxicities of the traditional systemic therapies -- and they are frustrated by the lack of access and ineffectiveness, and I think that's why, frankly, sometimes some of them have just plain given up.

And that's why, I think, even in an era with more therapies available, many patients -- more than a third with moderate or severe disease who could potentially benefit from treatment -- still end up without it.

So that is what I'm thinking about when I see these patients, but what did they tell me that they want? They want effective therapies that maintain clearance of psoriasis, therapies that are safe enough for

them to use for a long time, therapies that provide rapid response, and they want convenience with minimal disruption to their daily lives.

So in summary, on a personal level, it has been an incredible time to be working with patients with this disease and the therapies that have become available. It is a chronic, complicated, immunologic disease that we still do not fully understand, and on most days, I can count on being able to help people. But every day, I also work with patients who still need long-term solutions that keep them clear, healthy, and impact the rest of their lives in minimal ways, and that's why I felt it was so important to come here to tell you about where we are, and also where I think we need to go.

Thank you very much.

MS. GUZZO: Good morning, Mr. Chairman, members of the advisory committee, and FDA representatives. My name is Cynthia

Guzzo. I'm a dermatologist and vice president of immunology at Centocor, and it's my pleasure to review the efficacy of ustekinumab.

The proposed indication for ustekinumab is for the treatment of adult patients with chronic moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. To support this indication, I will briefly review the psoriasis clinical studies and the pharmacokinetics in immunogenicity across those studies.

Then I'll focus on the Phase 3 study designs and population, efficacy, patient-reported outcomes, efficacy in subpopulations, and finally, dose rationale. Using multiple measures, the data will demonstrate that ustekinumab is highly affective initially and over time for the treatment of psoriasis.

As Dr. Jones indicated, five clinical studies have been conducted to

support the psoriasis indication -- two Phase 1 studies, one dose ranging Phase 2 study, and two pivotal Phase 3 studies. Progressing through the program, the pharmacokinetic profile was developed, and together with the observed efficacy and safety, the dose rationale was progressively defined.

The Phase 3 dose regimens were based on the Phase 2 study for significant efficacy of four doses of ustekinumab compared to placebo, and a dose response across those four doses was demonstrated. The middle two exposures, 90 and 180 milligrams, were selected as initial doses in Phase 3 to achieve PASI 75 rates in the majority of patients, and were administered at two divided doses at week 0 and 4.

The lowest exposure, single doses of 45 and 90 milligrams, were chosen for maintenance. The Phase 3 maintenance dose interval of every 12 weeks was selected based

on the duration of response in Phase 2 after single doses of 45 and 90 milligrams.

In the overall population, a dropoff of response was seen after week 12 in the 45 milligram dose group. Similar responses were seen in subjects who weighed 95kg or less. However, in subjects who were over 95kg, a dropoff in response was seen in the 45 milligram group after week 8, and in the 90 milligram group after week 12. Therefore, an every 12-week maintenance regimen was chosen.

The pharmacokinetic profile was consistent across all studies. After subcutaneous injection Tmax occurred in eight days on average, subcutaneous bioavailability was approximately 60 percent. Cmax and AUC increased in a dose-proportional manner. The half-life was three weeks, consistent of that with a natural antibody, and a population pk analysis indicated that weight affected systemic ustekinumab exposure -- and I'll

discuss the clinical relevance of this later in the presentation.

In the Phase 3 studies, the incidence of antibody-positive subjects was low, approximately 5 percent, and remains stable over time. Slightly higher rates were seen in the 45mg group and in subjects who were over 100kg, and the highest rates were in subjects who received 45mg doses and were over 100kg, and they also tended to have lower serum trough concentrations.

There was a trend for lower serum concentrations and response in those who were antibody-positive, but antibody positivity did not preclude response.

Now I'd like to focus on the Phase 3 study designs. Efficacy data through at least 52 weeks in T08 and through 28 weeks in T09 was submitted. Through week 28, both T08 and T09 are identical in design. Additionally, both studies are five-year studies, and the data on the durability of

response and safety will be analyzed in the long-term extensions.

Today, I will be discussing three treatment periods -- the placebo-controlled period extending from week 0 to week 12, the active treatment and placebo crossover period from week 12 to week 40, and the randomized withdrawal period in T08 only from week 40 on.

In T08, 766 subjects, and in T09, 1,230 subjects were randomized. The demographics and baseline disease severity were consistent across each study, and while not shown, they were also consistent across the treatment groups in each study.

I would like to highlight several items. The mean body weight, ranging from 91 to 94kg, was high, typical of psoriasis patients -- medians are shown in parenthesis.

Subjects also had significant psoriasis with the psoriasis body surface area from 26 to 27 percent. At least

two-thirds of subjects had previously used conventional systemic or biologic agents, and finally, between one-quarter and one-third of subjects reported a history of psoriatic arthritis.

In the first study period in both T08 and T09, the placebo-controlled period, subjects were randomized to receive 45mg or 90mg of ustekinumab or a placebo at weeks 0 and 4. The primary evaluation instruments were the Psoriasis Area and Severity Index, or PASI, and the Physician Global Assessment, or PGA.

With the PASI, the evaluator quantitates the area of involvement, erythema, scaling, and induration in four body regions, with scores that range from 0 to 72 -- higher scores indicating more-severe disease. With the static PGA, the evaluator grades total body erythema, scaling, and induration, with scores that range from 0, cleared, to 5, severe.

The primary endpoint was at least 75 percent improvement in PASI from baseline at week 12, or PASI 75. Across the ustekinumab in both studies, from 66 to 76 percent of subjects achieved a PASI 75 compared to 3 to 4 percent in the placebo group. This was highly statistically significant.

The major secondary endpoint was a PGA of cleared or minimal. Again, high proportions of subjects across the ustekinumab groups in both studies from 60 to 73 percent achieved this endpoint compared to 4 to 5 percent in the placebo group. The PASI and PGA at week 12 reflect the substantial efficacy of ustekinumab after just two initial doses.

In the second study period from week 12 to 40, subjects initially randomized to ustekinumab received additional doses every 12 weeks, at week 16 and week 28.

The placebo group crossed over to

active treatment and received either 45 or 90mg of ustekinumab at weeks 12 and 16, equivalent to dosing in the initial ustekinumab groups, and then treatment every 12 weeks beginning at week 28.

PASI 50, 75, and 90 responses showing from left to the right in the figures were evaluated at week 28, the last common evaluation point in each study. Let me also point out that this was 12 weeks following the week 16 dose at ustekinumab trough concentrations.

The efficacy was remarkably consistent across both studies, with over 90 percent of subjects achieving a PASI 50, what has been defined as a clinically meaningful response, 70 to 79 percent of subjects achieving PASI 75, and approximately half of subjects achieving the high response of PASI 90. To remind you, the placebo group has already crossed over to active treatment, and I'll discuss their response momentarily.

And at week 28, high proportions of subjects also achieved a PGA of cleared or minimal from 59 to 61 percent in the ustekinumab 45mg group, and from 66 to 70 percent in the 90mg group.

This slide demonstrates the response over time through week 40 in T08 and through week 28 in T09 -- both the rate of response and the degree of response were again consistent across both studies.

Maximum response was achieved at weeks 20 and 24 in both studies and this was four to eight weeks after the week 16 dose. Responses declined slightly at week 28, and in T08, in the second treatment period from week 28 to 40, you see a replication of this dose response. We feel, notably, response was maintained at week 16, week 28, and week 40 at ustekinumab trough concentrations. We feel this periodicity indicates selection of an appropriate maintenance dose regimen every 12 weeks, and when the placebo group

crossed over to ustekinumab, they demonstrated a similar rate of response and degree of efficacy when compared to the originally randomized ustekinumab treatment groups.

Moving on to the third study period in T08, the randomized withdrawal began at week 40 when drug levels were at steady state and most patients had achieved their maximum response. Subjects who were non-responders at week 28 were discontinued, and partial responders at either week 28 or week 40 were adjusted to q8 week dosing. Only subjects who were consistent PASI responders at both week 28 and week 40 were randomized to either continue on ustekinumab every 12 weeks, or receive placebo -- in other words, withdraw from therapy.

Responders in the placebo crossover group were also withdrawn from therapy, and subjects were re-treated when they lost 50 percent or more of their PASI week 40

improvement.

The major secondary endpoint in the randomized withdrawal period was time to loss of PASI 75. Using a survival analysis, the percent of subjects who maintained a PASI 75 response over time at all visits was superior than the combined ustekinumab with every-12-week injections compared to placebo through one year, as was each dose compared to placebo.

Additionally, using multiple other measures, including PASI 50, 75, and 90, percent improvement in PASI and PGA of cleared or minimal, maintenance of response was consistently demonstrated in the ustekinumab treatment groups, with continual loss of response in the placebo groups.

Shown here in the figures were PASI 50, 75, and 90 responses which were maintained in the combined ustekinumab groups in green compared to a drop of response in the placebo group in red beginning as early

as four weeks after the first missed dose, with continual drop of response through week 60. Together, these analyses demonstrate clinically meaningful maintenance of response with every 12-week ustekinumab administration.

While the physician's assessment clearly demonstrated that ustekinumab is highly affective and will primarily serve as the basis for demonstrating efficacy, the patient's perspective is important. So consequently, across T08 and T09, multiple patient-reported outcomes were used. These included the dermatology-specific measures, including the Dermatology Life Quality Index and the Itch Visual Analog scale, and general measures including SF36, the Hospital Anxiety and Depression Scale, Work Limitation Questionnaire, and the Work Productivity Visual Analog Scale.

Across all these instruments, there was a statistically significant improvement

in the ustekinumab groups compared to the placebo groups at week 12, and when measured, they were maintained over time with ustekinumab treatment.

I'd like to focus for a minute on the DLQI, since it specifically evaluates the effect of skin disease on quality of life, and was measured through one year. The results in T08 demonstrated that by week 2, there was already a statistically significant difference in the change from baseline in the median DLQI in the ustekinumab groups compared to the placebo group.

And by week 12, there was a continual increase so that the mean improvement exceeded five, what has been suggested as a clinically meaningful improvement -- and with continued every 12-week dosing, the response was maintained at week 28 and week 40, and in the responders who continued on treatment, the response was maintained through one year.

While I've shown you data to support the efficacy of ustekinumab in the overall population using multiple endpoints, ustekinumab was also evaluated in multiple subgroups and was uniformly effective, including subgroups by administration method, demographics, disease characteristics, and previous treatment. Subjects were encouraged to self-administer at the investigator site.

After week 12, in both T08 and T09. PASI 75 responses were similar in the randomized withdrawal period in T08 -- in those who self-administered ustekinumab in blue -- compared to those who received injections from a health care provider in yellow.

To evaluate efficacy at week 12 in multiple study subpopulations, the treatment effect obtained by subtracting the PASI 75 response rate in the ustekinumab treatment groups from the placebo groups is shown along with the confidence intervals. The further

from the white line, the better the treatment effect, and with both doses, statistically significant and substantial benefit in all demographic populations was demonstrated. Similar findings were seen for disease characteristics, including severity classifications by PASI, PGA, and body surface area, and similar findings were seen when evaluated by previous treatments for psoriasis.

And now, as I told you earlier in the presentation, I'd like to focus on weight and its impact on efficacy. Weight actually factored significantly into the dose recommendation for ustekinumab for many reasons. First, it has been recognized that higher-weight subjects with fixed dose biologics have lower efficacy. Secondly, lower efficacy was observed in Phase 2 ustekinumab subjects over 95kg who received a single 45mg dose. I showed you that earlier in the presentation. Therefore, in Phase 3,

subjects were stratified by 90kg, which was the anticipated median weight, and two doses were studied -- in part to allow for the potential use of 90mg dose in the higher weight population.

And finally, an analysis of efficacy by 10kg increments was pre-specified to allow for more-accurate assessment of dose differences by weight. That analysis is shown here, with data from T08 and T09 combined. It's similar in both studies separately, and you can see that there was a larger dose response in subjects weighing over 100kg.

And when the 10kg increments are collapsed around the 100kg cut point in both the T08 and T09 study, the dose response for lower-weight patients in both studies is really negligible, but there was an obvious dose response for those who weighed over 100kg, approximately 20 points, between the 45mg dose and the 90mg dose.

Importantly, higher weight concentrations were correlated with increased efficacy. Data pulled from T08 and T09 show a concentration response relationship at week 28 -- as trough concentrations increase, shown in approximate quartiles at the bottom of the figure, the percent of subjects who achieve a PASI 75 and a PASI 90 response also increases.

Of note, serum concentrations are lower in subjects of higher weight over 100kg at either dose level. However, similar serum concentrations and efficacy were demonstrated with the two-step dose regimen, shown here by the serum concentrations in those less than or equal to 100kg who received the 45mg dose in blue, and the serum concentrations for those over 100kg who received the 90mg dose in yellow -- and you can see that the medium serum concentrations are similar in both of those groups, and that translates into similar efficacy in both of those groups.

You will hear from the FDA in their presentation that they have done an analysis of ustekinumab exposure/response relationship in T08 and T09, and they will discuss potential dosing considerations based on their modeling, including the two-step process that we proposed. Key findings in their analysis include the PASI 75 responses correlated with ustekinumab exposure, and that serum concentrations in AUC were less in heavier- than lighter-weight subjects, and we agree with this. They model dose adjustment of ustekinumab based on body weight, both by the two-step regimen we described -- at the 100kg cut point -- and they also modeled another three-step regimen, with a model dose of 67.5mg for subjects of intermediate weight between 70 and 100kg.

The predicted increase in PASI 75 response using this dose in these middle-weight patients was approximately 5 to 6 percent.

We looked at the actual dose response on PASI 75 responses between 45 and 90mg -- seen in the clinical studies in patients who were in these weight ranges. So in subjects who are less than 70kg, the dose response is negligible. Moving over to subjects who are 100kg or over, the dose response is substantial -- 17 percentage points between those who receive 45 and those who receive 90; however, with subjects between the ranges of 70kg and 100kg, there is no dose response, and that includes looking at the 90mg dose, since we did not use a 67.5mg dose.

Therefore, we agree that heavier patients over 100kg need 90mg, and light patients under 70kg can be treated with 45mg. However, mid-weight patients between 70 and 100mg gain minimal efficacy with additional ustekinumab exposure. Therefore, we feel a 67.5mg dose adds additional complexity and drug exposure with minimal efficacy

advantages.

After careful consideration of the multiple potential dose regimens, we continue to recommend the two-step process -- 45mg for those 100kg or less, 90mg for those over 100kg, which results in generally comparable serum concentrations of ustekinumab, and similar efficacy in both weight groups.

Consequently, the proposed dose regimen for ustekinumab is for patients weighing 100kg or less, the recommended dose is 45mg initially and four weeks later, followed by dosing every 12 weeks. For patients weighing over 100kg, the recommended dose is 90mg initially and four weeks later, followed by dosing every 12 weeks.

We believe this maximizes efficacy, minimizes drug exposure for patients, and reaches an optimum benefit/risk balance.

Dr. Yeilding will discuss in detail the safety data that support this dosing recommendation.

In conclusion, considering all the data presented, ustekinumab, after just two initial doses, is highly effective in improving psoriasis across multiple measures including PASI, PGA, and patient-reported outcomes.

Onset of response is rapid. Response is maintained through at least one year with every 12-week ustekinumab injections. Efficacy is established across all subgroups, including demographics, disease characteristics, previous treatment, and with self-administration, and the 90mg dose is more effective than the 45mg dose in subjects over 100kg.

I thank you for your attention this morning, and now I'd like to introduce Dr. Newman Yeilding. He's the senior director of immunology at Centocor.

Dr. Yeilding is the dermatology clinical team leader for the ustekinumab-psoriasis development program,

and he will review in detail the safety of ustekinumab.

DR. YEILDING: Mr. Chairman, advisory committee members, FDA representatives, good morning. My name is Newman Yeilding, and I will review the safety of ustekinumab.

In my review, I'll cover an overview of the analytical approaches used, review of the clinical adverse events, laboratory findings, more-detailed analyses of theoretical risks based on drug mechanism of action in psoriasis population risk, and finally, information from six months additional safety from our Phase 3 trials that was accrued after submission of our BLA, or Biological Licensing Application, in an overview of the safety across all indications studied.

The safety events targeted for additional analyses included serious infections and malignancy because of the putative role of IL-12 and 23 in pathogen

immunity and tumor surveillance. Additionally, since blockade of these cytokines may reciprocally up-regulate T-helper-2 cell or Th2, response rates of atopic diseases such as allergies and asthma were also evaluated.

The safety events targeted for additional analyses based on population risk were primarily selected based on relevant medical history of the study population. A high proportion of subjects had received prior therapies associated with an increased risk of skin cancer such as PUVA, cyclosporine, rates of cardiovascular risk factors were high, consistent with the burgeoning literature of the association of psoriasis and cardiovascular risk. Approximately two-thirds of patients had at least two cardiovascular risk factors, and one-third had at least three.

In the Phase 3 trials, 68 subjects with latent tuberculosis based on a positive

PPD and a negative chest X-ray were enrolled after initiating treatment with INH. Eight percent of subjects reported having asthma, and approximately a quarter had seasonal allergies, both potentially Th2-mediated diseases, and finally, 27 percent of subjects reported concomitant psoriatic arthritis.

In our Phase 2 and 3 psoriasis trials, a total of 2,266 subjects were exposed to at least one dose of ustekinumab. 1,602 subjects were treated for at least six months, and 362 subjects were treated for at least a year.

With the safety update that I'll provide at the end of my presentation shown at the bottom, over 1,200 subjects were treated for at least one year. The document provided to you by the FDA shows that this level of exposure exceeds by a substantial margin the ICH guidelines of 100 subjects exposed for a year. This large clinical development program was undertaken to provide

a large safety database because ustekinumab is a first-in-class agent with potential selective immunosuppressive properties.

Our strategy in examining clinical trial safety used two general approaches in evaluating rates of adverse events. First, rates of adverse events were compared between the placebo and ustekinumab subjects during the placebo control period when subjects were followed for similar periods of time.

The second approach examined rates of adverse events into controlled and uncontrolled periods of the study, where subjects who crossed over from the placebo group were included in the appropriate dosing group shown by the crossover lines.

In these analyses, event rates in the ustekinumab and placebo groups were compared after adjusting for time of observation, and are shown for 100 subject years of follow-up. And in my presentation, these will be designated by BLA or Biological

Licensing Application cutoff.

The data that I'll show include combined data from the Phase 2 and 3 psoriasis trials unless otherwise noted, and I'll provide a summary of safety across all indications studied towards the end of my presentation.

Shown here is an overview of safety during the placebo control period, showing rates of adverse events, treatment discontinuations due to adverse events, serious adverse events, and death. As you can see, overall, generally similar rates of these events were reported across treatment groups.

One death occurred in the 90mg group, and I'll provide more information on this subject later in my presentation.

The common adverse events that occurred in at least 2 percent of ustekinumab-treated subjects during the placebo control period are shown on this

slide. They were generally mild, self-limited and did not result in treatment discontinuation. There were no substantial differences between treatment groups, and a dose effect was not apparent. This pattern is also representative of the most common adverse events observed throughout the trials. And more information in other portions of the trials is provided in your briefing document.

Ustekinumab injections were generally well-tolerated -- 1.1 percent of injections were associated an injection site reaction, compared with 0.4 percent of placebo injections. There were no events of possible anaphylaxis or serum sickness-like reaction associated with ustekinumab.

Rates of antibodies were low, at approximately 5 percent, and were not associated with safety concerns. The rates of serious adverse events during the placebo control period were also comparable across

treatment groups. Most events occurred in only one subject in any treatment group. A table summarizing all of these events has been provided in your briefing document, and shown here are the events that occurred in at least two subjects, that included cellulitis, intervertebral disc protrusion, and hypertension.

Rates of serious adverse events through to the BLA cutoff are shown in this slide, which shows event rates adjusted for time of observation. The event rates that occurred at a rate of at least 0.1 per hundred subject years of follow-up are shown here, and this would approximate events that occur at a rate of at least one in 100 patients followed for a year.

As shown, there are no substantial differences between the placebo and ustekinumab groups.

Through the BLA cutoff, one death was reported in a subject in the 90mg group

who had a previously unrecognized idiopathic dilated cardiomyopathy and died from sudden cardiac death. Three additional deaths were reported after the BLA cutoff which resulted from alcohol intoxication and aspiration, post-operative hemorrhagic shock, and renal cancer. The rates of death observed in each study period were lower than expected based on 2006 data from the CDC National Vital Statistics Report.

Multiple analyses were conducted to evaluate the impact of cumulative drug exposure or cumulative duration of exposure on safety. Shown here are event rates in 16-week study periods. As shown, rates of adverse events, infections, and serious adverse events did not increase over time, and similar results were observed when adverse events were examined by cumulative milligram per kilogram exposure, or when the safety of maintenance therapy was evaluated in the randomized withdrawal period.

Overall, we observed no safety concerns associated with duration of exposure or cumulative drug exposure. Since the 90mg dosing yielded efficacy in higher-weight subjects, we also examined the impact of weight on safety. Shown here, rates of adverse events were comparable between treatment groups both within each weight stratum and across the weight strata -- and similar results were observed in analyses of serious adverse events and treatment discontinuations due to adverse events.

Subjects were encouraged to self-administer ustekinumab after week 12, and approximately 50 percent of subjects adopted self-administration by week 28. The rates of adverse events, serious adverse events, treatment discontinuations due to adverse events, infections, and injection site reactions were comparable between subjects who self-administered the drug and those in whom drug was administered by a

health care provider, suggesting no impact of self-administration on safety.

Turning to laboratory findings, blood counts and serum chemistries, including electrolytes, hepatic and renal panels, were monitored at each study visit, and in general, no impact of ustekinumab was observed on these parameters.

We also observed no substantial impact of ustekinumab on immune parameters, as measured by circulating T, B, or NK lymphocyte subsets, and no shift in the balance of Th1 and Th2 cells was observed in response to stimulation ex vivo.

And finally, in our Phase 1 trials and in primate toxicology studies, we observed no impairment of humoresponses to vaccines. So while the effects of ustekinumab on psoriasis were profound, we were unable to detect immune impairment with standard serologic or lymphocyte analyses or small vaccine studies.

Moving now to targeted adverse events, for these analyses including serious infections, malignancies, and cardiovascular events, I'll show event rates per hundred subject years of follow-up both for the control period and through the BLA cutoff.

The control period includes 20-week control period from the Phase 2 trial and a 12-week control period from the Phase 3 trials.

First, for serious infections, as a brief review of the theoretical role of IL-12 and 23 in infections, preclinical rodent models have suggested that these cytokines are important in immune responses to a broad range of pathogens, including viral, bacterial, and mycobacterial, parasitic, and fungal infections. Though emerging literature suggests that there may be important differences in IL-12 and 23 functions in rodents versus humans, understanding their roles in humans has been

facilitated by the identification of over 150 patients who are genetically deficient in both cytokines or their common receptor.

These patients demonstrated susceptibility to tuberculas and non-tuberculas mycobacterial diseases and to salmonella, but they appear to be susceptible to a narrower range of pathogens than predicted by mouse models -- specifically, they do not appear to be at increased risk for other pathogens, including common viral or other bacterial pathogens.

During the control periods of our clinical trials, overall infection rates shown here were comparable, at 1.70 and 1.23 per hundred subject years of follow-up for the placebo and ustekinumab groups respectively. Rates in the 90mg group were comparable to placebo, while rates in the 45mg group appeared lower, but this may simply reflect variability in view of the small number of events observed, and the

95 percent competence intervals shown in gray overlap for each group.

The serious infections reported in each group are shown on this slide. One potential opportunistic infection was reported in the 90mg group. A subject with herpes zoster with 19 vesicles outside the primary affected dermatome, but no clinical manifestations of visceral involvement were observed. All subjects responded appropriately to antimicrobials and recovered from their infections.

Through the BLA cutoff, rates of serious infection -- shown here -- again were comparable, at 1.65 versus 1.02 per 100 subject years of follow-up for the placebo and ustekinumab groups respectively.

It's notable that the high rate of mycobacterial diseases and salmonella observed in genetically-deficient patients was not observed in clinical trials of ustekinumab. In fact, no cases of

non-tuberculas mycobacterial diseases or salmonella have been reported throughout our clinical trial program. Moreover, in the one known case of TB exposure, the subject converted to a reactive PPD, confirming exposure, but did not develop an active infection. So overall, our clinical trial results do not reveal a serious infection safety signal.

Turning now to malignancies, I'll provide a summary of the pre-clinical data that suggests a theoretical risk, and additional information will be provided later by the FDA.

Preclinical rodent models suggest that IL-12 and 23 may have an impact on malignancy, though they may have opposing affects on tumors. IL-12 may elicit an anti-tumor immune response -- it may have anti-angiogenic properties, so blockade of IL-12 could be detrimental.

In contrast, pro-inflammatory and

pro-angiogenic affects of IL-23 and its impairment of anti-tumor T-cell responses, may promote tumor formation or growth. So it's been suggested that blockade of IL-23 could be beneficial in malignancy. Which of these opposing effects is dominant appears to be model-dependent.

Ustekinumab itself does not cross-react with rodent IL-12 or 23, so carcinogenicity studies or further meaningful assessment of ustekinumab in rodents is precluded. However, our primate toxicology studies show that no pre-neoplastic or neoplastic changes were observed with drug concentrations over 100-fold higher than that given to humans for up to six months.

Most patients who are genetically-deficient in IL-12 and 23 or their common receptors survive beyond childhood, but patients followed in this cohort were generally not older than the third or fourth decade of life, so limited

conclusions can be made about their risk for malignancies. However, it's notable that EBV-associated lymphomas have not been reported, supporting the notion that they may have limited risk from viral pathogens.

IL-12 has been evaluated as a potential therapeutic agent for human cancers, but studies to date have shown limited efficacy either as a single agent or when used as a vaccine adjuvant. Overall, our understanding of IL-12 and 23 biology today leaves uncertainty whether ustekinumab will have any effect on natural immune responses to tumors, or how it will affect the opposing balance between IL-12 and 23.

In our clinical trials, we examine malignancies in two general categories -- solid tumors, including all malignancies other than non-melanoma skin cancer, shown in the left panel, and non-melanoma skin cancers, shown in the right panel. During the control portions of the

trials, rates of solid tumors and non-melanoma skin cancers were comparable between treatment groups.

Shown again, through BLA cutoff, rates of solid tumors in the left panel and non-melanoma skin cancers in the right panel were comparable between the ustekinumab and placebo groups.

The solid tumors observed through the BLA cutoff included a hepatic malignancy in the placebo group, and in the ustekinumab groups, two cases of prostate cancer and one each of breast, transitional cell kidney cancer, and thyroid cancer.

For non-melanoma skin cancers, the ratio of subjects with basal versus squamous cell cancers was four to one, which is consistent with the ratio observed in immunocompetent patients, and does not reflect a reversal of the ratio that might be expected in immunosuppressed patients. So combined, these results are not suggestive of

a pattern of immunosuppression associated malignancies.

We compared rates of solid tumors with expected rates based on data from the 2004 Surveillance Epidemiology and End Results database, the SEER database, of the National Cancer Institute, adjusted for age, gender, and race. Shown in this slide are the expected number of malignancies -- shown in the purple bars -- and the observed number of malignancies in the gold bars for each treatment group.

The ratio of observed to expected events, called the Standardized Incidence Ratio, or SIR, was also calculated, and was 1.12 for the placebo group and 0.71 for the ustekinumab group. The ratio of less than one in the combined ustekinumab group indicates that the observed rate of malignancies was not higher than expected.

Overall, our analyses do not reveal a malignancy signal either in the rates of

events observed compared to the placebo or the general population, or in the pattern of events observed.

I will now review analyses of cardiovascular events, where I'll focus on major adverse cardiovascular events, including sudden cardiac death, myocardial infarction, or MI, and stroke. A more-detailed analyses of other cardiovascular events is provided in your briefing document.

In the Phase 2 trial, we observed a higher rate of cardiovascular events during the control period, though the randomization in this trial was also imbalanced at one to four.

Across the four ustekinumab arms, three events were observed -- two MIs and a stroke -- compared to none in the placebo group. This difference was not observed in the larger Phase 3 trials, with a single event reported in each of these larger

trials.

The risk difference observed in the Phase trial is shown in the right panel. This graph shows that the risk difference in Phase 2, the vertical yellow line, was greater than zero, with a 95 percent confidence interval -- shown in the horizontal yellow line that overlaps zero.

Estimates in the Phase 3 trials in the combined Phase 2 and 3 data, shown at the bottom of the graph, illustrate that as more data were accumulated, the risk difference closely approximates zero or no difference. And overall, these results show the difference observed in the smaller Phase 2 trial was not reproduced in the larger Phase 3 trials.

In multiple additional analyses, we consistently observed that inclusion of greater amounts of our clinical trial data progressively attenuates the difference that was observed in this Phase 2 trial.

The incidence of major cardiovascular events during the control period and through the BLA cutoff is shown in this slide. The control period shows graphically the data I just reviewed. And consistent with the previous analyses, when all data through the BLA cutoff are considered, event rates were comparable in the placebo and ustekinumab groups, at 0.55 and 0.61 events per 100 subject years of follow-up, respectively.

MI and stroke rates were further examined by partnering with investigators from the Framingham Heart Study to develop a predictive model that allowed for estimation of the number of events that would be expected after adjusting for relevant cardiovascular risk factors, including cholesterol, blood pressure, diabetes, and smoking history.

And depicted in this slide are the expected number of events -- shown in the

purple bars; the observed number of events shown in the gold bars -- for each treatment group.

SIRs were also calculated and demonstrated that the observed rates were consistent with expected. Combined, our analyses show that the higher rate of events observed in Phase 2 is progressively attenuated as we accumulated additional data, and overall do not reveal a cardiovascular safety signal.

Finally, I'll provide an overview of analyses that examine the potential impact of ustekinumab on asthma, psoriasis, and psoriatic arthritis. Analyses of asthma and other atopic diseases did not reveal any safety concerns. No serious adverse events of asthma or treatment discontinuations due to asthma were reported in ustekinumab-treated subjects, and the adverse events of asthma were uncommon, and responded appropriately to therapy. Adverse events of

seasonal allergies were also uncommon, occurring in less than 1 percent of ustekinumab-treated subjects. And no worsening of atopic dermatitis was reported in ustekinumab groups.

Psoriasis and psoriatic arthritis adverse events were also uncommon, and there was no evidence that ustekinumab worsened these conditions. And moreover, there was no evidence of rebound psoriasis observed in the clinical trials.

Since the BLA cutoff, a Safety Update Report was completed that contained six months' additional safety data from the Phase 3 trials, which increased overall exposures by approximately 50 percent. A summary of the additional safety experience is provided in your briefing document, and a summary of the targeted events is provided in this table, showing that rates of serious infections, major cardiovascular events, and malignancies remain stable or decrease

slightly with the additional safety data.

As Dr. Jones indicated, we studied ustekinumab in other diseases, including psoriatic arthritis, Crohn's disease, and multiple sclerosis.

In these populations, no new safety signals were observed. And as shown in this slide, rates of targeted events across all indications were generally comparable between ustekinumab and placebo-treated subjects when adjusted for follow-up.

So in summary, the safety experience with ustekinumab derives from a large clinical development program, including 2,316 psoriasis subjects -- with 1,285 subjects treated for at least a year, and 373 for at least 18 months.

In our clinical trial experience, safety was comparable between treatment groups, and we observed no dose effect on safety. We believe that the data demonstrated that ustekinumab is safe and

well-tolerated.

Combined with the efficacy results provided by Dr. Guzzo, we believe that these results demonstrate that ustekinumab has a favorable benefit/risk profile in patients with moderate to severe psoriasis who are candidates for phototherapy or systemic therapy, and justify the dosing proposed in Dr. Guzzo's presentation.

Ustekinumab was highly effective in treating this severe disease, while in both general and targeted analyses, safety signals with ustekinumab were not apparent. The rates of serious infection, malignancy and major cardiovascular events observed in our trials was consistent with the expected rates.

We believe that the size of our clinical trial database, the duration of observation of one to one and a half years in our two large Phase 3 trials, the high level of efficacy, and the lack of safety signals

provide a solid basis for approval of ustekinumab. Nonetheless, we recognize that our database cannot exclude an impact of ustekinumab on uncommon safety events or theoretical risks such as malignancy or serious infections, and Centocor is committed to continued data collection to address these theoretical concerns.

We've incorporated plans that will continue to define and manage ustekinumab safety post-marketing, including continuation of our T08 and T09 studies for five years of treatment, and a comprehensive risk management plan. And Centocor has a history of successfully delivering on these commitments.

So in summary, based on the data we've reviewed today, we believe that ustekinumab has a favorable benefit/risk profile.

I would like to thank you for your attention, and I will now introduce Dr. Peter

Callegari, vice president of our medical affairs group, who will provide an overview of our plans for continued assessment of ustekinumab safety in our risk management plan.

Thank you.

DR. CALLEGARI: Mr. Chairman, members of the advisory committee and the FDA, I'm Dr. Peter Callegari, and I will share with you our risk management plan.

Centocor believes ustekinumab has a favorable benefit/risk profile. We've based this belief on a number of factors. There was a large clinical trial safety database, with over 2,000 patients studied, representing one of the largest programs for a biologic agent in psoriasis.

A definitive safety signal in the clinical development program has not been identified. And we've developed a comprehensive risk management plan to prospectively monitor the safety profile of

ustekinumab in the post-marketing setting.

That said, we've identified topics based on theoretical or postulated concerns for which we plan to perform additional surveillance post-approval. The first two topics -- malignancy and serious infections, as described earlier in this presentation by Dr. Yeilding -- have been chosen because of a theoretical concern based upon mechanism of action related to the inhibition of IL-12, 23.

The third, cardiovascular events, was chosen due to the high prevalence of cardiovascular risk factors in the psoriasis population. The next, serious systemic hypersensitivity reactions, is a theoretical concern with all protein therapeutics. And the last topic, exposure during pregnancy, was chosen not because of a known or even theoretical concern, but rather for the unknown effects of ustekinumab on the developing fetus.

Elements of what I will present today represent an extension of our original plan, and are not fully described in the briefing document. We have expanded our proposal, based on the advice and critique of the FDA, to utilize available large health care databases to supplement our proposed risk assessment efforts. This approach is modeled on the FDA's Sentinel initiative.

Centocor has developed a risk management plan to maximize the benefits and to minimize the risk of ustekinumab use. The components of this plan are risk assessment and risk minimization activities.

The primary purpose of risk assessment activities is to gather safety data about the use of ustekinumab. We will utilize larger patient populations to detect infrequent events, longer patient follow-up, pharmacovigilance, and epidemiologic methods, and multiple robust data sources.

We are proposing a broad-based

database strategy for obtaining additional safety data. The goal of the assessment program is to access or create data sources with known denominators, and critical data elements capable of identifying the potential associations between ustekinumab use and the theoretical risks.

Each data source, clinical trial extensions, spontaneous reports, health care data sets, and targeted prospective registries, will be employed to maximize capture, and efficiently and effectively identify potential signals as early as possible. Taken together, these data sets represent the substantial proportion of U.S. psoriasis patients.

This approach would assure a large portion of patients exposed to ustekinumab are identified and available for analysis, without the potential issues associated with a large mandatory registry effort.

It's also important to remember

that the estimated number of psoriasis patients treated with each of the currently approved biologics ranges from approximately 2,000 to 50,000 patients.

This is a schematic representing the elements we will use in a comprehensive safety signal assessment program to evaluate the stated theoretical concerns. Signal detection is the process to detect the possible drug-related risk. Signal replication corroborates the possible signal in another dataset, and further characterizes the signal using comparative data.

Signal detection and signal replication occur in parallel. Evaluation is the process of testing for the signal that you've identified.

Building further on this theme, we will use data from clinical trial extensions, clinical trials and new indications, pharmacovigilance and spontaneous reports, health care claims data, registries and

cohort studies, and health care data with record access, to detect or strengthen or corroborate a possible signal.

The signal that you've identified is subsequently evaluated using formal or observational clinical studies. And I'll discuss this in more detail.

As you've heard, we will be collecting long-term safety data from several clinical trials as an aspect for signal detection. Perhaps most importantly, the ongoing open label, long-term extensions of the Phase 3 trials, T08 and T09 -- as discussed earlier by Dr. Guzzo -- will be conducted over a period of up to five years.

Starting with almost 2,000 patients and assuming an attrition rate of approximately 10 percent per year, an estimated 7,500 patient years of follow-up will be obtained.

An ongoing etanercept comparator study in psoriasis will provide additional

ustekinumab safety data compared with that of the currently approved anti-TNF therapy for psoriasis. We plan to study ustekinumab in other indications, allowing a better understanding of the safety profile of ustekinumab patients in patients with other complex immunologic diseases. And finally, we plan to conduct a meta-analysis of the clinical trial data, evaluating identified topics of interest.

Centocor and J&J have a comprehensive pharmacovigilance system already in place. Adverse events are systematically collected as single cases, reviewed by safety physicians, and collected into a centralized safety database. The aggregate adverse events are examined routinely for patterns, such as change in frequency, severity, and the types of events reported -- for example, specific malignancies.

The detection of changes in

reporting patterns enables us to establish the safety profile of a product, and to implement appropriate risk minimization strategies, such as labeling changes.

Centocor, in partnership with the FDA, has successfully identified, investigated and appropriately warned about risks detected through the pharmacovigilance system.

The next element of signal detection is the use of health care databases. Using these databases, we can efficiently and accurately identify patients with psoriasis under treatment, including those treated with ustekinumab. The theoretical concerns that we've identified are potentially rare, but if they do occur, should be identifiable in medical claims data.

The incidence rates as well as strength of association between the drug and the outcome can be rapidly assessed with

these datasets.

PharMetrics is an example of a large, multi-source claims database. It does not offer access to source medical records, but it's a useful illustration of how claims data can be used in safety surveillance for adverse events of interest.

The PharMetrics Patient-Centric Database is the largest independent claims data source in the U.S., containing nationally representative data drawn from over 90 health plans. There are currently approximately 300,000 psoriasis patients, 5 percent, or 15,000 of whom, may require biologic therapy. In addition, there's potential for longitudinal patient exposure and outcome data.

Importantly, data from all patients enrolled in health plans that are part of the database are captured, removing bias that might be related to selective enrollment in a strictly voluntary registry.

This dataset can also be used to screen for AEs of interest in a population with a known denominator of exposure.

While some pregnancy outcomes research can and will be undertaken in claims data, a specific pregnancy registry is being proposed to evaluate this population of special interest. This study is a five-year-plus prospective observational cohort study of pregnancy outcome data obtained from the Swedish, Danish, and Finnish medical birth registers. These databases are currently being used in an ongoing pregnancy study for another Centocor product.

In this study, all women with psoriasis who have been exposed to ustekinumab during pregnancy, as well as all pregnant women with psoriasis who are not exposed to ustekinumab, will be identified. Psoriasis therapy from three months prior to conception through birth will be captured.

Pregnant women with prenatal exposure to ustekinumab will be compared to pregnant disease-matched patients and to healthy pregnant controls.

The health status of infants with prenatal exposure to ustekinumab will be followed prospectively for one year after birth. Outcomes collected will include malformations at birth, and rates of infection in newborns through the first year of life.

I will now discuss our proposed elements of signal replication, that is the corroboration of a possible signal in another dataset and the further characterization of that signal using comparator data, recognizing that some of these databases could also be used for the full evaluation of a signal.

The Nordic Database Initiative is an example of a dataset that we will use for signal replication. It's a prospective