FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE MEETING (DODAC)

Silver Spring, Maryland

Wednesday, June 18, 2008

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SHEILA RITTENBURG

CAROL WALLACE, M.D.

LESLIE WATKINS

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P R O C E E D I N G S

(7:58 a.m.)

MS. WAPLES: Good morning. We're about to begin. Can you please take your seats?

DR. BIGBY: Good morning. My name is Michael Bigby, and we will commence the committee meeting on etanercept for pediatric psoriasis.

For topics such as those being discussed 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 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 topic during breaks or lunch. Thank you.

At this point, I'd like the members of the Committee, and those sitting at the table, to introduce themselves.

DR. STRAHLMAN: Dr. Ellen Strahlman. I'm the industry representative, and I work at Pfizer.

DR. SHWAYDER: Dr. Tor Shwayder, pediatric dermatologist, Henry Ford Hospital in Detroit, Michigan.

DR. RINGEL: Eileen Ringel. I'm a

dermatologist in Maine.

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

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

DR. LEVIN: Arthur Levin, consumer advocate, Center for Medical Consumers in New York City.

DR. THIERS: Bruce Thiers, Department of Dermatology, Medical University of South Carolina in Charleston.

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

DR. MAJUMDER: Mary Majumder, consumer representative from Baylor College of Medicine.

DR. O'NEIL: Kathleen O'Neil, pediatric rheumatologist, University of Oklahoma in Oklahoma City.

DR. STERN: Robert Stern,

dermatologist, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston.

DR. KATZ: Robert Katz, dermatologist, Rockville, Maryland.

DR. KETTL: Dave Kettl, medical officer, Division of Dermatology and Dental Products at FDA.

DR. AVIGAN: Mark Avigan, director, Division of Adverse Events, Office of Surveillance and Epidemiology, FDA.

DR. MATHIS: Lisa Mathis, associate director, Pediatric and Maternal Health Staff, Office of New Drugs, FDA.

DR. WALKER: Susan Walker, director of the Division of Dermatology and Dental Products, FDA.

Just before we go on, I'll make a correction to the meeting roster. Under the FDA Center for Drug and Evaluation Research participants, the names will be amended to reflect the folks sitting here at the table.

DR. BEITZ: I'm Julie Beitz, director,

Office of Drug Evaluation 3 in CDER.

MS. WAPLES: Good morning.

The Food and Drug Administration, FDA, is convening 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 are 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 the Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 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 U.S.C. 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 a particular individual's 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 with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of 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 U.S.C. 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 103795/5350, Enbrel, etanercept. 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 interests and 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 represent 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 discussions involve 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.

I would 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 her.

DR. BIGBY: We're going to do the open public hearing first.

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

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

For example, this financial

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

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

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

dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair.

Thank you for your cooperation.

Susan.

DR. WALKER: Good morning. I'd like to welcome the Committee members back, and also the new members that are joining us today. And we really thank you for taking the time from your busy schedules to participate. We know this represents a significant amount of time away from your primary duties.

Today, we'll be asking you to discuss another application pending before the agency. Amgen proposes approval of a currently marketed biologic therapy, etanercept, to be used for the treatment of pediatric plaque psoriasis. While there are several biological therapies approved for adult plaque psoriasis, there are no biologic therapies currently approved for pediatric plaque psoriasis.

We'll be asking you to provide advice and discussion concerning whether or not there's sufficient information to support the approval of etanercept for use in children with psoriasis. We'll ask you to discuss the specific benefits and risks of therapy, and to provide advice and recommendation on whether the product works, does it keep working, and what are the long-term risks.

We'll ask you to determine if there is adequate information on short-term safety and on long-term safety, and are additional data needed either before or after approval.

As this is the first application for approval of a systemic biologic therapy for the treatment of pediatric plaque psoriasis, your recommendations today will help guide the Agency in determining the quality and quantity of information that should be submitted prior to approval of a systemic biologic therapy for this pediatric

indication.

We'll also be asking you to comment on the degree and severity of psoriasis that should be studied for systemic therapy, the optical study design to provide a sufficient pre-approval safety database, and the impact, if any, of the outstanding etanercept post-marketing safety studies.

Thank you.

MS. WAPLES: OPA Speaker No. 1?

Thank you.

MS. LARSON: You can change it to the next slide. Thank you.

Good morning. My name is Kelsey Larson, and I have no financial relationship with any pharmaceutical company, including Amgen.

The National Psoriasis Foundation assisted me and my mother's travel to this hearing. I am from West St. Paul, Minnesota, and I am 16 years old. I was diagnosed with psoriasis at 4-1/2, and cannot remember my

life without it. Although I try not to let it get the best of me, it has an impact on my daily life.

Slide. I went through the whole spectrum of medications, including topical steroids, UVB therapy, and even ignoring my disease. Some of the medications I used are now banned by the FDA, such as Skin Cap. None of these made a significant dent in controlling my psoriasis.

Slide. At the end of eighth grade, I decided I needed to take the treatment of my psoriasis a little more seriously, and went to three dermatologists for opinions. They all independently said Enbrel would be the best treatment option.

In addition, I visited a rheumatologist to see if I had psoriatic arthritis. If I had arthritis, that meant that getting Enbrel would be much easier, because it is approved for juvenile arthritis patients. Honestly, a small part of me hoped

that I did have arthritis so I could get Enbrel.

Slide. I always knew psoriasis was chronic, but for some reason, I either thought that that did not apply to me or I just did not comprehend what chronic meant. I can still remember one of the dermatologists looking me straight in the eye and bluntly saying that with a case like mine, I would have it for the rest of my life. This hit me hard. I still remember sobbing with my mom on the car ride home.

Slide. About six months later, I had my biggest outbreak ever. I was about 60 percent covered, and in constant pain. I would cry myself to sleep because I felt as though my skin was on fire.

The only thing that even began to help the pain was putting ice packs on my body. I could not wear make-up because I would look like a circus clown. For a freshman in high school, this is a hard

reality to face.

I am also a dancer. My psoriasis made it very hard for me to make it through a whole dance class without crying because my skin was in so much pain. With a blanket of raw skin on your body, moving and bending is not very easy.

Slide. Winter was also not enjoyable. My skin is generally much worse in the winter, and to have it so bad at that time made being outside a lot harder, which is something you cannot avoid when you live in Minnesota. At this time, I began seeing a new dermatologist, who worked harder than anyone should have to work in order for me to have a better quality of life.

He worked to get Enbrel approved for me. Because of my age, it was difficult to get the approval, even though I had failed light therapy, and topicals were not successful.

I finally began Enbrel on March 6,

2006. By March 20, my face was already clearing up, and I could see skin emerging from the psoriasis that covered my abdomen. I have now been on Enbrel for two years. My doctor did discuss potential risks with my mom because I am a minor. However, I was not really concerned with them because I just wanted something that would work, and was willing to live with whatever came along with it.

This past summer, I realized how much my body relied on the drug. I was overseas with my grandma and left my shot at home, thinking that skipping one week in the summer wouldn't be that big of a deal. On the day I was supposed to administer my shot, I got itchy all over and had to use Benadryl to relieve the itching. Since then, I have had to up my dose.

When I started Enbrel, it was in a prefilled syringe, and my mom gave me the shots. Last summer, I started using the

auto-injector. I am now responsible for my own treatment. It is also much easier to administer since I do not see the needle.

Slide. During my big outbreak and struggling with getting Enbrel, I had lost all hope, and thought that I would be stuck in that physical state forever. Even once I got the medication, I was skeptical, because nothing else had worked. I have now completely disproved myself. Enbrel has given me hope that I can have clear skin. Being able to dance comfortably again is also incredible. It is also enjoyable to be able to wear black and not worry about my flakes showing up everywhere.

If my skin had not improved so much, I really don't know where my life would be today. Participating in golf at school would be more painful. Going to my junior prom this year was awesome, but without Enbrel, I would not have been so confident, nor would I have been as physically

comfortable. I had no worries that my itchy skin would bleed, or that I would have to clean up flakes off my dress.

The approval of Enbrel would prevent other young psoriasis patients from going through the hassle I had to endure and allow them to live life to the fullest.

Thank you.

DR. SHWAYDER: Mr. Chairman, may we ask questions of the presenter?

DR. BIGBY: Sure.

DR. SHWAYDER: Kelsey, thank you for your wonderful presentation. I'm a pediatric dermatologist, so I see patients like you every month, if not every week, in my practice. And actually, I need to ask a question of your mother since I would probably be asking this of your mother. Is she there with you?

MS. LARSON: Yes, she's right here.

DR. SHWAYDER: So I'll have to give you a little flavor of the Sophie's Choice we have to make with this sort of discussion.

So, Mrs. Larson, I'm your dermatologist and I have this wonderful new drug which I'm going to give you for your child's psoriasis. And it's convenient. You're given a shot and it's going to make all her psoriasis go away. However, in 20 years, she has a 100 percent risk of lymphoma. Would you use it?

A simple yes or no. I have a series of back-up questions after this.

So 20 years from now when she's 35 she has a 100 percent of lymphoma. Would you chance it?

MS. WATKINS: At 100 percent, probably not.

DR. SHWAYDER: Let's say it's 50 percent risk. Fifty-fifty chance of getting lymphoma in 20 years.

MS. WATKINS: That would be something to discuss together with us and to find out more about lymphoma. We did discuss that at the time -- when we decided to go forward with this

treatment.

DR. SHWAYDER: What happens if I made it 10 percent?

MS. WATKINS: I would risk it.

DR. SHWAYDER: Because no side effect is rare to the person who has it.

MS. WATKINS: That's right. When it's you, it's 100 percent.

DR. SHWAYDER: Right. So now what happens if I tell you, gee, Mrs. Larson, there's this sort of data out there that says maybe it's going to give you lymphoma but I can't put a number on it? Maybe it's 0.1 percent. Maybe it's 1 percent. Maybe it's 10 percent. How do you handle that as a mom, and it's your kid, and then you might not see grandchildren?

MS. WATKINS: As a mom, I have a child now. And I would take that risk.

DR. SHWAYDER: That's all I need to know. Thank you. That was really wonderful.

MS. LARSON: Thank you.

MS. WAPLES: Thank you.

OPH No. 2?

MS. RITTENBURG: Good morning. My name is Sheila Rittenburg, and I'm the senior director of Advocacy and External Affairs for the National Psoriasis Foundation.

The Foundation receives financial support from thousands of individuals each year, and from 12 pharmaceutical companies, that provide unrestricted funding, including Amgen and its competitors.

I'm speaking to you today on behalf of the National Psoriasis Foundation. We're the nation's leading psoriasis patient advocacy organization -- and on behalf of the community it represents, to testify in support of the approval of etanercept for the treatment of moderate to severe psoriasis in the pediatric population.

I'm also speaking to you today as someone who experienced severe psoriasis as a child. I was four when I developed psoriasis. The disease confused, frightened,

and frustrated my family. My treatments consisted of thick layers of ointments, of cream applied daily, and black, smelly, coal tar baths. If you're ever tried to get a four-year-old to do anything he or she doesn't want to do, you understand what my mother went through to treat my psoriasis. We even made our way to Florida from Canada each winter to keep me clear and comfortable for at least a short time.

As I grew into adolescence, I spent hours a day on my psoriasis. My skin and scalp were unsightly. I was accustomed to being taunted or shunned, and my self esteem took a dive. In addition to the usual physical indignities of adolescence, I had large patches of plaques all over my body. What's worse, none of the treatments really worked.

What I would have given to have been free from a life of treatment regimens that didn't amount to much. We needed the

option of making a different kind of treatment -- a different kind of choice about a different kind of treatment. But there were no other choices. And if you now fast-forward some 50 years and look around, it's not much different today for children with psoriasis. Fifty years, and we don't have much more to offer kids.

We do know a lot more about psoriasis. It can occur at any age, including early childhood. Data from Psoriasis Foundation surveys of over 3,000 respondents found that almost 34 percent of our constituents were diagnosed before the age of 19. As many as 7.5 million Americans have psoriasis, and approximately 1.5 million have moderate to several disease. Those patients are often in constant pain and have trouble with normal daily activities such as sitting at a desk, playing ball, or even walking.

Plaques can cover significant

portions of the body, and when they are thick, burning, cracking, and bleeding, any small action can be painful.

Long considered a mere skin rash, recent studies show that psoriasis patients, because of their psoriasis alone, are at increased risk for other serious diseases such as heart attack and diabetes. Up to 30 percent of patients have psoriatic arthritis, a painful condition that impairs functioning.

What's more, studies show that psoriasis causes as much disability as other major medical diseases such as cancer, hypertension, heart disease, and diabetes. What this means for children is that adolescents and teens already struggling with social interactions, already challenged with progressing at school and finding their place in the family structure, are also dealing with a debilitating and demoralizing disease.

I would like to paraphrase from a

parent's e-mail that I think highlights just how serious psoriasis is for kids.

This mother says, my son was diagnosed with psoriasis at the age of 4, and psoriatic arthritis at 10. He has episodes of severe psoriasis that cover approximately 50 to 70 percent of his body. These conditions have affected his activities greatly over the years, to the extent of him having to be placed on homebound education through the public school system due to his inability to physically keep up with the fast pace of school, complications pertaining to his impaired immune system due to the medications he receives, and weakness in his knees and hands.

In studies of adults, rates of suicidal ideation are higher for psoriasis patients, and depression is high. It's a frightening prospect to think about how youth and teens, for whom self esteem and depression are issues at the best of times,

will handle being shut down by a disease that isolates, embarrasses, and leaves you feeling hopeless.

We also know just how profoundly psoriasis impacts patients' quality of life. Our surveys determine that half of children under 10 find psoriasis to be a significant problem in everyday life. The extreme burden pushes people to take great personal risk in finding effective treatments.

For example, patients report trying medicines not approved in the United States, enrolling in clinical trials to test unproven treatments, or staying on drugs that are known to have risks if used long- term. At the same time, patients are concerned about long-term safety of any biologic for psoriasis, and whether for adult or pediatric populations.

So are dermatologists. I had the opportunity of attending the advisory meeting here yesterday on approval of ustekinumab.

One of the Committee members referred to the cavalier use of biologics in general. And I have to respectfully disagree. Many of us are parents. We don't jump to decisions lightly when it comes to using drugs like etanercept for our kids. And actually, the culture of dermatology is a cautious one, too. If anything, the uptake on biologics for psoriasis in the dermatology field has been low. Our surveys show that almost half of respondents are under-treated for moderate to severe disease.

With the possibility of etanercept being approved for psoriasis for kids, patients will need to work with their doctors to understand and balance risk and benefits. The Foundation supports plans that further the understanding of the risks involved and potentially mitigate them.

Not all families will opt for their children to be treated with this medication, but they have a right to that option when

pain, anguish, and distress are what make up their kids' lives.

Therefore, we're asking you today to give children with psoriasis, their families, and their doctors, an important new tool in the fight to control this serious disease. Children with psoriasis deserve a normal childhood. More effective treatment options will give them just that.

Thank you.

DR. MAJUMDER: This is Mary Majumder. I have a question. So this drug, unlike the drug we discussed yesterday, is already out there on the market and can be accessed, although it's not approved for this use. Could you comment on the difference approval will make? Say a little bit more about perhaps insurance coverage issues that your constituents currently encounter because it's not approved for this use.

MS. RITTENBURG: Do we have all day? In the best of circumstances, even for adults,

coverage is a challenge. Health plans and their policies are all over the map. Depending on the structure of the plan, some people have access to drugs like etanercept with a very modest co-pay. For others, it's prohibitive. For kids, we have had to work with our constituents and sort of fight on their behalf to get approval for the drug for people like Kelsey.

We imagine if this drug is approved that it will be very closely scrutinized by the health plans. We anticipate additional barriers might be inserted into the process, making it even more difficult to access.

Does that answer your question?

DR. BIGBY: Thank you.

DR. LEBWOHL: Good morning. I will have the most unusual conflict of interest statement that you've heard because I'm here to speak in support of an Amgen drug, and their competitor, Centocor, paid for my trip.

My name is Mark Lebwohl. I'm chairman of the Department of Dermatology at

Mount Sinai, and I have been a speaker and consultant for Amgen and for most of their competitors that make psoriasis products. My department does clinical trials for Amgen and gets grant support from Amgen and from most of their competitors.

I'm speaking today as chairman of the Medical Board of the National Psoriasis Foundation, and I'd like to start by reading a letter that I asked a patient to write for this Committee.

"I can't remember not having psoriasis. What I remember most is the stigma of growing up with psoriasis. I remember girls not holding hands with me at school. Sometimes they wouldn't hold my hand. Sometimes I was just so self-conscious, so afraid of rejection, that I wouldn't hold their hands. I remember going to school with a greasy head because of the messy ointments I used to treat psoriasis in my scalp.

I remember wearing sweatpants and long sleeves on 100-degree days in gym so that other kids wouldn't see the psoriasis on my arms and legs. I remember dirty looks at the town pool. I remember kids making fun of me in school and on the bus.

The worst part about that was that my little sister got in trouble for slugging a kid on the bus because he made fun of me. That feeling that I couldn't take care of myself was the worst part of this.

I was lucky enough to marry a wonderful wife. When we had kids, I prayed every day that they wouldn't get psoriasis so that they wouldn't have to go through what I went through. Every day, I would look at their skin and their scalp with anxiety and in trepidation. Every day I feared that they, too, would develop this disease that has plagued me my entire life."

His two sons, unfortunately, developed psoriasis. One of them badly on

the face and scalp.

But no child should have to suffer the way that he did. Surveys by the National Psoriasis Foundation and by others report approximately 10 percent of patients with psoriasis contemplate suicide.

Our patient surveys indicate overwhelming dissatisfaction with currently available therapies.

From the point of view of a physician taking care of psoriasis patients, I worry a lot about side effects. The most common treatment I use for severe childhood psoriasis is ultraviolet B phototherapy. And ultraviolet B phototherapy will remain the most common treatment I use for severe childhood psoriasis even if this drug is approved.

But what can I do for a child with severe psoriasis that doesn't respond to UVB? What can I do for a child who can't take off three times a week from school to get their

UVB light treatments?

I have treated a small number of children with cyclosporine because of severe disease, but I worry about their kidneys. And the current guidelines limit me to one year of treatment with that.

I've seen a small number of children treated with methotrexate, but I worry about their livers and their bone marrows. Remember that taking even aspirin can raise their methotrexate levels, or many of the non-steroidals that are available over the counter can raise their methotrexate levels and damage their bone marrows. There are deaths from methotrexate every year.

Etanercept does not cause the major organ toxicity that methotrexate and cyclosporine do. But insurers -- to answer your question -- will not let me prescribe it for children most of the time because it is not approved for pediatric psoriasis. So I usually cannot get it for children.

The advantage, if there is an advantage to an injectable medication, is that patients -- parents and children -- are more cautious with an injectable medication, and are less likely to easily accept it without looking into it more carefully. So their questions about the side effect are much greater than if I just prescribe a pill, even though the injection might be safer than the pill.

I'm asking you to put yourselves in the shoes of these unfortunate kids. Give me, their physician, one additional tool to treat them.

Thank you.

DR. BIGBY: Thank you. The open public portion --

MS. WAPLES: OPH No. 4.

MS. LEWIN: Good morning. My name is Malia Lewin, and I'm a CEO and executive director of the International Psoriasis Council.

IPC is an international non-profit

organization of dermatology professionals dedicated to advancing psoriasis education, research, and treatment. Our organization represents dermatology professionals from 17 different countries, who treat thousands of patients worldwide.

I have no personal conflicts to disclose. As an organization, IPC receives unrestricted educational grants from many private and corporate resources, including Amgen and all of its competitors.

Psoriasis is a serious immune-mediated chronic inflammatory disease that requires lifelong care. For the 2 to 3 percent of the global population suffering with this disease, psoriasis carries substantial physical and psychological burdens.

From our perspective, these burdens are equal to or greater than those held by patients with ischemic heart disease, diabetes, and chronic obstructive airways

disease. For the 10 percent of patients who present before the age of 18, we believe that these burdens weigh even more heavily.

Among other measurements, perhaps the most compelling is that suicidal ideation in young people with psoriasis is twice that of their peers without psoriasis. The normal challenges of self esteem, body image, and fitting in with one's peer group become exponentially greater given the visibility of psoriasis. Clearly, something must be done to help these patients, especially those with moderate to severe disease. These patients have the greatest need and the fewest available options.

It is the International Psoriasis Council's position that the Committee should recommend approval for the use of etanercept in the treatment of psoriasis for the pediatric population.

Children eligible for systemic therapy generally should be eligible to

receive etanercept. IPC encourages continued long-term study of these agents to better understand long-term risks, but view the extended label as a necessary and valuable advancement.

Thank you.

DR. PARANZINO: I promise to be brief since you heard from me yesterday. But this issue is too important -- this issue of how to treat children with psoriasis and how to treat them effectively. So I want to say a few words.

My name is Mike Paranzino. I'm the president of Psoriasis Cure Now, which is a non-profit patient advocacy organization based in Bethesda. And just to reiterate the conflicts -- Psoriasis Cure Now has received unrestricted funding from Amgen and some of its competitors. And I also have a personal conflict in that I have two nieces with significant psoriasis. So your decision today and in future years is likely to directly impact their well-being.

I also want to commend you on yesterday's hearing, which was a tour de force. I was exhausted just watching it, so I'm sure you folks must have been exhausted from battling it out. But your decision and work, including the FDA, will certainly help patients for years to come.

We heard in yesterday's hearing, and we heard from Kelsey and Dr. Lebwohl and the others, how devastating psoriasis can be. We heard it yesterday in adults, and it can even be worse for children. Kelsey in fact is so poised that it almost gives you a mis-impression of how she's dealt with it so successfully that it might diminish the reality out there that I hear from parents about how some children are not doing the way she's doing and are truly troubled and isolated and withdrawing into their homes.

Terribly heartbreaking stories.

What adds to the challenge for parents is finding appropriate treatments.

As Dr. Lebwohl mentioned, and as we saw in the briefing materials we've seen from the adverse event reports, children on cyclosporine, children on methotrexate, prednisone, biologics, Enbrel, Remicade -- these are tough choices. It's which black box are you going to subject your child to, or which black boxes? Those are some of the toughest decisions that a parent would have to face.

But that said, as between the mother and the parents making the choice, or a Committee and the FDA decision for every child across America, I think we have to empower those families and their physicians to make those calls -- those decisions.

I'm a fan of the FDA. In fact, I was at a hearing like this defending them after the Vioxx issue arose at a similar DODAC. But I was disappointed to read in the briefing materials one sentence about the impact of psoriasis on children -- that it's

not a life-threatening disease in childhood, and complications are rare and largely psychosocial.

Again, that strikes me as diminishing the full impact, and certainly not giving full credence to how devastating psychosocial impacts can be, particularly on children.

It's because of those impacts -- it's the physical pain, to be sure. It can be itch, which can be ferocious. And the psychosocial impacts that can lead to depression and despair and harm a child's education and their sense of worth that extends long beyond their childhood years. That is why we support your approval of Enbrel for the pediatric population.

It's an interesting position you're in because it is available off-label. In fact, a rejection now would make it that much harder to access it, because insurers would have a wonderful way to deny coverage -- to

point to a FDA rejection. So we're in a curious position where some children have successfully -- thousands according to the briefing materials -- have successfully accessed biologics like Enbrel off-label. And your decision today could actually make it more difficult.

On the alternative, an approval would aid with coverage, and also lead to more research. Wouldn't it be nice if this -- I guess it was a Congressional act that encouraged this study to occur -- if this encouraged other companies to study their treatments in children, because it's been -- it adds to the difficulty for a parent to not have research on children when they're making these decisions with their physician.

They hear, well, it's been studied in adults. We have no data on children. That just adds to the trouble and the challenge.

The study did show -- I think it was at 48 weeks, that it was clearly effective. And safety was demonstrated for that year. I agree that we do not want to be frivolous with the use of biologics in children -- Enbrel -- or adults. Enbrel and the other biologics are not appropriate for many patients with psoriasis. But for some children with psoriasis, it's essential to their well-being and their health.

So I look forward to learning a lot today, and I again appreciate the time and the work that you do.

DR. BIGBY: Thank you. Lynn.

DR. DRAKE: Mr. Chairman, I'd like to apologize to you and everybody in the room for being late.

For the record, my name is Lynn Drake from Massachusetts General Hospital, Harvard Medical School. By way of justification, there was a flood in my house. And it happened yesterday, but the insurance

company called me as I was walking out the door, and I must admit they took a little bit of priority. So please accept my apology.

DR. BIGBY: Do we have more?

DR. SHWAYDER: I actually had a question for Mr. Paranzino. And I was wondering if your group would support amnesty from lawsuits for physicians using Enbrel in children for unknown long-term risks.

MR. PARANZINO: I am an attorney, but I'm not a practicing attorney. And I'm a critic of the trial lawyers, although some of them do give us funding. I don't ask them what cases they --

DR. SHWAYDER: Give me a carte blanche so I don't have to worry about it.

DR. PARANZINO: You bring an important part up, which is a rejection of this will make you more subject to liability and will make it that much harder for a family to get a dermatologist to prescribe Enbrel, because then you would go into court -- perhaps if there is

an adverse event down the road -- and you will have acted in opposition to a stated FDA and/or Advisory Committee decision. So by this proposal, you are in a tricky spot.

DR. BIGBY: I think there are no more open hearing speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

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

The floor is now open to the presentation by the sponsor.

DR. EISENBERG: Good morning, Dr. Bigby, Committee members. I think the public session has framed the issues that we need to consider today.

I'm Paul Eisenberg. I'm responsible for Amgen's global regulatory affairs and safety organization. I'll just

make some brief opening comments to frame the issues from Amgen's perspective that we'd like you to consider in your deliberations.

The first is as noted in the briefing book. This study was undertaken as a post-marketing commitment as part of the Pediatric Research Equity Act. For those of you who are not familiar with this Act, the intent is to provide access to pediatric populations for therapies that are show efficacious in adults. Etanercept in the decades since its approval has shown substantial efficacy in adult and pediatric rheumatic diseases, as well as adult psoriasis.

I think it's also important to note, and it was commented on, that there are no systemic therapies -- immunologic therapies including biologics, but not limited to biologics, that are approved for pediatric psoriasis.

Our interest in pursing the

challenging studies of enrolling patients in this type of program, as well as the challenges that have been discussed for this indication are based on the input we've had from pediatric dermatologists in particular -- and we've heard some of that this morning in patients -- that there is an important unmet medical need for additional therapy in pediatric patients with moderate to severe psoriasis.

To remind you, etanercept is a dimeric fusion protein. It consists of the extracellular binding receptor for TNF, which is bound to a Fc portion of IgG1 to prolong its half-life. Molecular weight is approximately 150,000 kD. And the mechanism of action is it acts as a decoy receptor for TNF, so it binds the soluble TNF, and thereby prevents it from binding to its cellular receptor, where it would be active.

Etanercept was approved initially almost a decade ago based on substantial

efficacy in moderate to severe rheumatoid arthritis. And that efficacy subsequently was translated to the value in pediatric populations for juvenile rheumatoid arthritis. The approval for the psoriasis indication which we're discussing today in adults was in 2004 for moderate to severe plaque psoriasis.

Our experience with etanercept is unusually large for a biologic. In the 10 years since it was approved, it has actually been studied in over 25,000 patients, so we have the opportunity to consider a fair amount of randomized double-blind control data. We have over 1 million years of patient-year experience in the post-marketing environment.

So there is a substantial database, some of which is highlighted today by FDA in terms of post-marketing adverse event reporting. And in addition, there is a robust pediatric exposure of almost 28,000

patient-years.

What we'll be discussing this morning first are the results of our pivotal trial, which demonstrated substantial efficacy of etanercept in 4 to 17 year olds with moderate to severe plaque psoriasis. We will be reviewing our safety experience in general across indications in the pediatric population, both in clinical trials and post-marketing experience, and our experience briefly in the post-marketing experience with adult psoriasis.

There are concerns that have been highlighted both leading up to this meeting. Recently, a FDA advisory around the potential of malignancy for the TNF blockers as a class across indications. And there obviously are concerns with the TNF agents in the decade since etanercept was approved with regards to serious infections, many of which are confounded by concomitant therapies.

And we look forward to discussing

those with you and having you consider the overall benefit-risk.

It is clear that the benefit-risk in this population is different than the other pediatric indications of juvenile rheumatoid arthritis. And accordingly, we will be proposing a risk management program which also includes a safety registry, to continue to gain important safety information should you advise FDA that an approval is appropriate.

In terms of our presentation, Dr. Lawrence Eichenfield will follow me and talk briefly as a pediatric dermatologist about pediatric psoriasis, and then Dr. Michael Severino of our clinical development group will speak about our clinical experience and post-marketing experience with Etanercept.

And I'll come back and talk briefly about the risk management program and some closing comments.

Thank you.

Dr. Eichenfield.

DR. EICHENFIELD: Thank you, and good morning. I'm Larry Eichenfield, a pediatrician and pediatric dermatologist from Rady Children's Hospital and University of California San Diego. I've had a long interest, career interest, in inflammatory skin disease in children. So what I would like to do today is give an overview of psoriasis in the pediatric and adolescent age group, to discuss the approaches we take to therapy -- how we have to balance risk and benefits in our options for therapy, both topical and systemic -- and to discuss specifically this population of moderate to severe patients, and some of the clinical needs that we have in treating their psoriasis.

So as I start off, we've had some very eloquent testimony of the impact of psoriasis on individuals this morning already, but I thought I would discuss a patient who we just saw in our practice a

week and a half ago. Has a history of psoriasis. Has been through phototherapy on two occasions. Has been on topical therapies in the past, and was asking for something more. Asked what we could do to handle his disease. And went on to tell me about how this disease has impacted on him -- his decision about what he's going to wear. Or whether he's going to go with his friends to the beach. Very significant impact on this individual.

There's another one of my patients, a 17-year-old who has moderate psoriasis present on her back and also on her legs. And I don't think you can see the facial psoriasis on her photo, but I don't think that's as important as the fact that she has a face of psoriasis. And in fact, if you take away the HIPAA-compliant eye shields that I placed in -- you know, she'll look at me in the eye and relate to me how this has had so much impact on her life -- her

relationship to her friends; her concern when she goes to school. Her concern about getting a job.

Here is a younger child, a 7-year-old with severe psoriasis. You can see the hyperkeratosis and the erythema. You can also see the very trendy Hulk underwear that he's wearing.

This is a 13-year-old. I'm just showing you a portion of her body. Just her face. And you can imagine the impact that this can have on someone's life. How other people will look at this, wondering what is this? Is this infectious? Can they catch it? And clearly, a tremendous impact when you speak to patients about this disease.

Psoriasis is a chronic inflammatory disease of the skin. We know it presents -- manifests with a sharply demarcated, thickened red plaques. To a degree also, though, psoriasis is an inflammatory disease. It can be associated

with markers of inflammation, with arthritis. And there's clear evidence, not just anecdote, about the significant morbidity and disability that can be associated with it.

The presentation of psoriasis in pediatrics is similar to adults, in that most psoriasis is plaque psoriasis, seen in up to 84 percent of individuals. There tends to be a lot of face and intertriginous involvement in children, but it can be on any part of the body, and very commonly on extensor surfaces as well.

There are other forms of psoriasis, including Guttate psoriasis, which can be triggered by strep infections, as well as pustular erythrodermic psoriasis and nail disease, which I'm not going to discuss this morning.

The pathogenesis of pediatric psoriasis -- I understand there was a little discussion on psoriasis in yesterday's panel, so we'll keep this brief. Essentially, the

pathogenesis is similar to that of adult psoriasis. We know that there's T lymphocytes and cytokines which mediate the disease, and that the necrosis factor can promote both keratinocyte proliferation as well as proinflammatory cytokines and impact vascular endothelial cells as well.

The prevalence of psoriasis -- there is actually stronger data in adults than in pediatrics. We have about 2.2 percent of adults diagnosed with psoriasis, and estimates are about 25 percent of those have moderate to severe disease. When it comes to pediatric psoriasis, it depends how you get at the numbers. There have been several studies that have asked adults who have psoriasis when did your psoriasis begin. And about a third of patients will report that it begins during childhood.

And then there are some other data. Gelfand did a study out of the U.K. giving

estimates of about .55 to 1 percent of the pediatric population. It's my sense, and in talking to other pediatric dermatology specialists, that the rate of moderate to severe disease -- the percentage is lower in the pediatric age group than it is in adults, that it may be only 10 to 15 percent who have moderate to severe disease.

And to skip ahead, it's only a subset of those that cannot be maintained with topical therapy. However, there is a subset that can't be maintained with topical therapy. And there's this population that has a tremendous need for therapy.

But when we talk about psoriasis severity, how do we quantify it? And this is actually -- this is a difficult issue. The American Academy of Dermatology had a consensus statement where they said that quantification of severity is to a degree a qualitative decision, because it hinges on a variety of different measures -- the disease

activity, resistance to therapy, the type and locations of the lesions, the response to different medication symptoms, pain and itching, and then quality of life considerations. And we'll go through some of those.

In the clinical studies that will be reviewed later, the etanercept studies, we used pretty static measures of severity. The PASI score, which is a psoriasis area and severity index, is essentially measuring how much psoriasis, and what's the quality of psoriasis on different parts of the body. And then summing it up together.

And the global score, the static physician global assessment, actually is only looking at lesions. It's sort of describing what the majority of lesions are like. Those aspects of severity don't define the persistence of the psoriasis, the course of the psoriasis, or the symptoms.

Now, we have clear evidence in

adults on the physical and psychosocial impact of psoriasis. Forty percent of patients report problems with everyday life due to their psoriasis. Adult reports of fatigue, depression, and suicidal ideation, and in a well-designed survey, 51 percent of respondents reported having significant life disruptions and social withdrawal.

How about in pediatrics? Well, there's a very well-designed study by Beattie and colleagues that looked not at just impact of psoriasis -- it was really a study looking at chronic disease in children and measuring how they reported the impact of the disease on their lives.

And if you look at this graph on the left -- in the orange, that's healthy, which is pretty much baseline, saying that healthy kids -- you know, their quality of life defines the baseline. But if you look at psoriasis at 9.2, its impact was reported -- impact on the quality of life for

the affected individuals with psoriasis exceeded that of seizure disorders and diabetes, and was only outstripped in this study by chronic asthma.

So from a quantitative measure as well, there's really a tremendous perceived impact of the disease on the quality of life in the pediatric-aged patients.

In the etanercept trial, there were questions that assessed pediatric-like quality.

And if you look at the baseline results, the scores of the patients in that trial showed similar impact on quality of life to those reported of children with JRA. And there's clearly data on symptom complex impacting on sleep, school, work, and leisure activities.

Now, psoriasis has associated comorbidities associated with it. Psoriatic arthritis can be seen during childhood. More commonly in adulthood. There are no good

prospective trials to follow pediatric patients into adulthood to look at the relative time course of that, though in psoriatic arthritis studies generally, arthritis is preceded by 10 years of cutaneous psoriasis. In the etanercept study, about 10 percent of the patients actually had arthritis at the time of enrollment.

Obesity, atherosclerotic heart disease, myocardial infarction, and metabolic syndrome are clearly comorbidities that are seen in adult patients, and some of those risks extend down to young adults. So for instance, in the Gelfand paper looking at risk of myocardial infarction, myocardial infarction is higher in patients with psoriasis. And it's actually higher in the subgroup of younger adults.

So a 20- to 30-year-old had a 3.2 relative risk of a myocardial infarction as compared to a patient who didn't have

psoriasis.

We do not have pediatric data on these comorbidities, and it would be interesting to study it in the future. And it's clearly unknown how psoriasis treatment may impact on the development of these comorbidities over time.

So when I have those patients in the office, like the patient who I said came a week and a half ago or the one from several months ago, how do I treat the patient? How is it that dermatology specialists go after this disease? We start off with topical therapy. Not just approved therapies, because there's a very restricted armoraterian (?). There are basically only two topical corticosteroids that have approval for psoriasis: a low potency and mid-potency topical corticosteroid.

But we use a variety of other agents, including mid-potency to high-potency topical corticosteroids, topical vitamin D

drugs, tars/anthralins, tazarotene, a variety of other treatments, most which do not have specific indication. And to be truthful, a significant percentage of pediatric psoriasis patients do find or get by with topical therapy.

The problem is that there's still the subset that don't get by with topical therapy and have an incredible need for something beyond that. And then we get into systemic therapy, and none of the systemic therapies have been especially well-studied in terms of having a good evidence basis. We have phototherapy. We do have approved devices with phototherapy. It's a standard intervention. When it comes to the immunosuppressive medicines, we really don't have a good evidence basis, though we use them.

We regularly will use methotrexate or cyclosporine in psoriasis. Prednisone is used, though most dermatology specialists are

scared of prednisone. You can get rebound flares with it. Systemic retinoids, not used commonly -- and biologic agents -- I'd like to discuss a few of these in more detail, because these are the alternatives that we go to with these patients.

So phototherapy, both narrowband and broadband UVB light are used. But there are concerns even with these. And I'm quoting the standard reference text in Pediatric Dermatology to give sort of a sense of where the field is in summarizing this.

It says although data are lacking in children with psoriasis, recurrent exposure to UVB may increase the long-term risk of the development of skin cancer and premature aging.

And when it comes to PUVA therapy, it's actually not very commonly used in pediatric and teenage patients because of concerns of ocular toxicity, photosensitivity, and the risk of development

of actinic changes and cutaneous carcinomas.

Methotrexate is also used as an unapproved treatment for pediatric psoriasis. Its indication is for RA, JRA, and severe adult psoriasis. Actually, its safety and efficacy in pediatrics is really restricted to cancer chemotherapy and JRA.

Methotrexate has a high rate of side effects as well as potential toxicities. Nausea, fatigue, headaches, and anorexia are common. And there's one adult randomized clinical control trial -- a very well-designed trial of methotrexate as compared to cyclosporine -- and when you look at the rates of the side effect profiles with those medicines, they're pretty high. In that paper, you know, 44 percent of the adults reported nausea as part of their symptom complex with the use of methotrexate.

Probably of more concern in children and adolescents are the potential toxicities. Hepatotoxicity and bone marrow

suppression being very significant concerns. Infections, potential malignancy. We know that methotrexate is an abortifacient, and teratogen. There's a need to avoid vaccines. And of course, there's a significant amount of laboratory monitoring as we assess whether when we use these medicines if there's any organ damage that's happening with its use.

Cyclosporine is also unapproved but also used. Its indication is for adult patients with severe plaque psoriasis who have otherwise normal immune systems. Clearly, cyclosporine is a potent immunosuppressant and has a large set of potential adverse events: hypertension, nephropathy, headache, hepatotoxicity, hyperlipidemia and infections.

And in that same New England Journal Heydendael paper where they did the randomized controlled trials compared to methotrexate, 33 percent of individuals reported paresthesias of the fingertips and

toes.

Malignancy risks are very significant with cyclosporine in the pediatric and adolescent age group, with leukemias, lymphomas, and skin cancers.

And quoting again from Paller's textbook, "other oncogenic risks are heightened with childhood use." There's a need to avoid live vaccines. And similar to methotrexate, there's a need for routine laboratory monitoring because of the many end organs that can be affected by the medicine.

Retinoids are also not approved but are occasionally used in pediatric and adolescent patients -- less commonly, because they're less effective as a monotherapy. Generally used for exfoliative erythrodermas or pustular psoriasis.

Significant set of side effects and toxicities: hyperlipidemia, hepatotoxicity. It's an abortifacient and has particular issues with that because it can remain in the

system for three years even with a single use.

So when it comes to taking care of the patients we have in the office with moderate to severe disease who have made it beyond topicals and the topicals aren't holding them, how do we approach these patients? And it's really a risk and benefit analysis.

This is a talky slide, but it's out of the British Journal of Dermatology. Chris Griffith's statement says, with moderate to severe disease, we generally will use phototherapy or systemic agents. Then it goes on to say, "however, potentially serious toxicities can limit their long-term use." And because there's no standard therapeutic approach, you have to discuss risk and benefits and weigh these with your patients, individualizing the potential risks with the potential benefit from patient to patient.

Now, as a pediatrician and

pediatric specialist, I really like the Pediatric Research Equity Act because it asks for drugs to be studied in the pediatric age group -- requiring studies of new drugs -- if there's potential, meaningful, therapeutic benefit -- that can represent an improvement in the treatment or diagnosis or prevention of disease in the pediatric population, and there's a need for additional options.

So please, the Act is there. And in this case, etanercept was taken up in this context and studied. We've added -- remember, we started with 10 years of pediatric experience with etanercept in other conditions, but there was no real evidence basis for its use in psoriasis. We didn't really have any controlled clinical trials for psoriasis in children and adolescents.

And this is a reproduction of the images from Amy Paller's and colleagues' publication in the New England Journal, that

reported the results of the core clinical study. And you can see impressive results, PASI scores that go from 21.6 to 7.6 in a 6-year-old, and a 35.2 to 1.0, giving us an evidence basis for this medicine.

But, I know that -- you know, tonight I fly back to San Diego and probably within a day or two I will see patients such as these who come in with psoriasis. It's not that common a population, but there's a population that can't be well-maintained with a topical therapy. And we're going to have a risk benefit discussion -- I will with the patient and with the family -- about the relative risks and relative toxicities of the medicines that we have. Regardless of what the Committee does today, we're going to have to have those discussions. Whether it be phototherapy, methotrexate, cyclosporine -- and I think that from a physician's standpoint, a family standpoint, and a patient standpoint, the consideration

of having options for these patients who have these significant needs would be reasonable.

Thank you.

DR. SEVERINO: Thank you, Dr. Eichenfield.

Dr. Bigby, members of the Committee. My name is Michael Severino, and I'm responsible for clinical research in the area of inflammation at Amgen.

It's my pleasure to be here today to speak with you about the use of etanercept in children with moderate to severe pediatric plaque psoriasis.

I'll begin by discussing our controlled clinical trial. I will then walk you through some of the broader etanercept safety experience, with a particular emphasis on the use of this agent in children. I will update you on our ongoing evaluation of malignancy, and conclude with some special considerations for the use of etanercept in children.

I'd like to start by orienting you to our pivotal trial in pediatric psoriasis. This trial was conducted in three phases. The first was a randomized double-blind comparison at 12 weeks, which was intended to serve as the primary demonstration of efficacy.

The next phase was an open-label period in which all subjects received etanercept for an additional 24 weeks. The purpose of this phase was to look at durability of effect, and also to gain additional safety data.

The third phase took patients who had a good clinical response, PASI 75 at week 36, and randomized them to receive either continued etanercept or a placebo in a double-blind manner. The purpose of this study was to examine the impact of stopping therapy on patients, because we know that psoriasis may be treated intermittently.

In addition, there were a number of

escape arms that were felt necessary to ensure the ethical conduct of the study. In the first escape arm, patients who had an early worsening of their disease received open-label etanercept. In addition, there was an incomplete responder arm that patients entered at week 24 if they failed to achieve a PASI 50 response, and at week 36 if they failed to achieve a PASI 75. In this incomplete responder arm, patients were eligible to receive additional topical therapies for their disease.

Lastly, in the withdrawal phase, the third phase of the trial, patients who lost PASI 75 were crossed over to open-label etanercept.

Major inclusion criteria are shown here. Subjects are between 4 and 17 years of age and had disease for at least six months. Although, as Dr. Eichenfield pointed out, there is no broadly accepted definition of moderate to severe plaque psoriasis, for the

purposes of this study, we used a Physician's Global Assessment, or PGA score, of at least 3, at least 10 percent body surface area involvement, and a PASI score of at least 12 at baseline. In addition, patients were required to have failed topical therapy or received prior photo or systemic therapy for their disease.

Major exclusion criteria are also shown here. There were limitations on the use of topical steroids. Patients should not have received systemic or phototherapy within 14 days of entry. They should not have received systemic biologic agents within 30 days, and should have had no prior exposure to etanercept or other TNF blockers. In addition, patients with recent or recurrent infections were excluded.

If we look at the primary and secondary efficacy measures, the primary endpoint was PASI 75.

That is a 75 percent improvement on

the overall PASI scale at week 12. Secondary and other measures included other levels of PASI response and PASI at other time points, mean PASI improvement, PGA score.

And we had a quality of life measure --the Children's Dermatology Life Quality Index.

If we look at baseline demographics, we can see that they were generally balanced between groups. If we look at the age distribution, I'll note that we had a preponderance of older children in the trial. Approximately two-thirds were between 12 and 17 years of age.

This next figure shows a little bit more information about baseline distribution of age for all subjects. Again, you can see that the majority or children were between 12 and 17 years old. And you can get a little bit more information about the distribution.

We're also showing distribution of weight using age and sex adjusted percentiles

at baseline.

And again, as noted in the briefing material, subjects were heavier in this trial than their age and sex matched peers. This is perhaps not surprising given the association of increased BMI with psoriasis, at least in the adult population.

If we look at baseline disease characteristics, the mediation duration of disease was approximately six years. The groups were all matched with respect to the extent of their skin disease. Somewhat more subjects had psoriatic arthritis at baseline in the placebo group at 13 percent when compared to the etanercept group at 5 percent.

If we look at prior therapies, we see that approximately 30 percent of subjects overall had used prior systemics. The most common of these was methotrexate. If we look at the combination of systemics or phototherapy, more than half of subjects in

each group had received these treatments.

This next figure gives some more information on the baseline distribution of disease severity as measured by PASI. The median was approximately 16, but as you can see, we enrolled subjects with a wide range of disease activity at baseline.

This next table gives you a summary of patient disposition during the double-blind and second phase, the open period of the study. Overall, there were very high rates of completion during the double-blind portion of the trial, with over 99 percent of subjects completing. In addition, 208 subjects entered the open-label portion of the study, and 171 completed it.

This next figure shows the efficacy results at the primary time point for comparison, week 12 of the first phase of the study. As you can see, there was considerable clinical response across all levels of the PASI scale. If we look at the

primary endpoint, PASI 75, we see that this level was achieved in 57 percent of subjects in the etanercept group as compared to 11 percent of subjects in the control.

I'll also note that 27 percent of subjects in the etanercept group achieved a PASI 90 response, and the PGA response shown on the far right of this figure agreed very nicely with PASI 75.

Some but not all members of the Committee will have experience using the PASI score in clinical trials. So here, I've shown representative pictures of response. Across the top are pre-treatment pictures. The bottom images are post-treatment. And these are all subjects who are enrolled in our trial. Beginning from the left, we have a PASI 50 response; in the middle, PASI 75; and on the right, a PASI 90.

This next figure now incorporates data from the second phase of the trial. The open-label period that extended to week 36.

Here we show PASI 75 over time. And I'll call your attention to a few points. The benefit that was seen in the double-blind portion was maintained over time in the original etanercept group. As you can see, PASI 75 levels remained in the 60 percent range. And the original placebo group had a very nice response after being crossed over to open-label etanercept at week 12, as shown by the yellow arrow.

This next graph shows a similar pattern now looking at PGA clear or almost clear status. Again, in the original etanercept group, the benefit was maintained over 36 weeks, and a very nice response was seen in subjects who were crossed over from the original placebo group at week 12 -- again shown by the yellow arrow.

We did include a quality of life measure in our trial. This is the CDLQI, or Children's Dermatology Life Quality Index. And although the sampling time points were

less dense here, I think you can appreciate that the shapes of the curves are very similar to what I showed you before. There was a statistically significant benefit when compared to placebo in the CDLQI measure, and that benefit was maintained over time.

I'd now like to spend a few minutes discussing the third phase of the trial -- the randomized double-blind withdrawal and retreatment period. As I mentioned in my introduction a few minutes ago, the purpose of this portion of the study was to examine the effect of stopping etanercept therapy in subjects who had a good response, because it's recognized that psoriasis may be treated intermittently in the course of routine clinical practice.

At the time we designed this trial, however, there was also concern that cessation of therapy might lead to abrupt worsening, or perhaps even rebound. Based on this, we set a very low threshold for

retreatment, and allowed retreatment at very early time points, as early as week 4. As I mentioned before, subjects entered this phase of the trial if they had a PASI 75 response at week 36. They entered open-label treatment, which represented a crossover from placebo to therapy in the randomized placebo group, and a change from blinded etanercept to open-label etanercept if they had any single value less than PASI 75 at any time point.

Again, just to illustrate the threshold that we've used here, I have representative photos from a subject at two visits within this trial. On the left, we have the time point where that subject had a 76.8 percent improvement from baseline in PASI, so he would have met PASI 75 criteria. And on the right we have another visit, where the patient had 74.2 percent improvement from baseline. As you can see, the level of clinical response and biologic effect of the

drug is largely maintained in both photographs.

DR. SHWAYDER: Can I ask a question? Go back to that slide. So you mean the person on the right would have been bumped into --

DR. SEVERINO: The person on the right would have been bumped into the treatment arm since he was less than 75 percent. So this is the same person at two time points. On the left, that person would have been continued on therapy. On the right, the person would have been defined as a failure by the criteria in the study, and entered open-label treatment. Not only would that person have entered open-label treatment, but they would have been counted as a permanent failure based on a time to event analysis.

DR. SHWAYDER: The PASI -- it's an analog, not a digital thing. You kind of Gestalt it -- like 5 percent here. A little red, little scaly. And yet you have it down to one decimal point here.

DR. SEVERINO: I agree that we should look at this from a bigger picture point of view. If we say it's generally 77 and 74 percent, your point is well-taken. The score is a continuum. PASI 75 is a categorical cut of that. And on either side, there is not much clinical difference between -- for example, 77 and 74. As I mentioned before, these were very conservative rules to try to avoid children getting worse in the course of the trial.

DR. SHWAYDER: I understand. And it's like half the kids got this better, according to your graph. Fifty, 60 percent.

DR. SEVERINO: Fifty-seven percent at the primary endpoint. That's correct.

DR. SHWAYDER: So it's 40 to 50 percent did not get this better.

DR. SEVERINO: Forty-three percent at week 12 didn't achieve this level. Many achieved PASI 50 level of response.

DR. SHWAYDER: Okay, thank you.

DR. SEVERINO: So your point is

well-taken given the nature of the continuous variable here. And I'll talk about that a little bit more in a second.

DR. KATZ: You mentioned over 50 percent --

DR. BIGBY: Can we question him after the presentation?

DR. SEVERINO: So if we use the definition or retreatment or crossover to open-label etanercept that I just described, we do see that more patients met that definition in the placebo group as compared to the etanercept group. And the numbers are shown here: 29 in the placebo group and 13 in the etanercept group.

If we then plot a time to event analysis -- and here, I have reproduced the analysis from the FDA's briefing materials -- we have done a very similar analysis and our results agree. We see these curves separate. There are a couple of important points to make here. One is that

the curves that all patients in both groups were receiving etanercept up to week 36. So it would take time for their disease to worsen. And as I mentioned before, we had very conservative rules, and they were assessed at week 40 and week 44, and were considered failures if they had any single value below 75. So the fact that we see separation here is evidence for a continued treatment effect of the therapy.

In addition, the shape of the etanercept line itself has caused concern among some reviewers that there may be a waning of biologic effect of the drug. We believe that this is due to the very conservative rules we set for retreatment just around the PASI 75 threshold, which was required for entry and exit from the group. And I'll show you some data to illustrate that in just a second.

The way to illustrate the impact that this threshold effect has on the results

of this portion of the study is to look at PASI as a continuous variable. Here, we plot percent improvement in PASI from baseline as a continuous variable. And again, we see that the lines separate. The difference between the lines is not great. However, we had all patients again treated up to week 36, and instituted therapy as early as week 40 or 44.

If we look at the green line, we can see more clear evidence of continued biologic effect of etanercept. Here, I plot some additional data to make this point. This is a group of 31 subjects who are also shown in the FDA's briefing materials. These subjects were selected because they received etanercept continuously over the course of the trial, from week 0 to week 48.

Again, I'm showing PASI as a continuous variable -- that is mean percent improvement in PASI over the course of the study. And again, you can see in this group

that there is maintained biologic effect over time. Now, we recognize that this is a highly selected set of patients; however, if we repeat this analysis with all of the patients in the randomized withdrawal and retreatment period, or with all of the patients in the study, we see the same results.

I would now like to discuss the safety experience from our pivotal trial. If we look at the double-blind period and compare the percentage of subjects with various adverse events, we see the following. Overall, adverse events were reported not infrequently, but were generally balanced between groups. This is also true of non-infectious adverse events. It's important to note that none was serious, and very few led to withdrawal from treatment.

If we look, however, at infections, we see a slightly different pattern, with the rate of reporting of infections being

somewhat higher in the etanercept group at 47.2 percent, as compared to the placebo group at 31.4. Again, it's important to note that none of these infections was serious, and none led to withdrawal from the study.

If we look at the specific terms that were reported most frequently within the study, they are generally consistent with what would be expected in an ambulatory patient population of this age, and also consistent with the general patterns that I described to you on the prior slide.

Not shown here because it occurred at less than 5 percent -- I'll also discuss briefly streptococcal pharyngitis, which was reported more frequently in patients in the etanercept as compared to the placebo group. Here, we have 2.8 percent versus 1 percent in the double-blind period.

If we look at the adverse event summary over the full 48-week duration of the trial, we see very similar results. Here,

we've switched to reporting rates to account for the mismatch in exposure between placebo and etanercept. These reporting rates are calculated by taking the total number of events divided by the patient-years of exposure, and normalizing to 100 years.

Overall, non-infectious adverse events accounted for about half of the total. However, serious events were uncommon. There was only one reported in the etanercept group. This was a benign hemorrhagic ovarian cyst in a 14-year-old girl in the trial. And very few led to withdrawal from the trial.

If we look at infections, we see that overall infections, non-serious infections reported non-infrequently; however, serious infections were uncommon. There were three terms reported as serious. However, these correspond to two clinical episodes in two patients. One patient had gastroenteritis and an associated term of dehydration, both of which were reported as

serious. The other patient was a 7-year-old with history of asthma who had a lower lobe pneumonia that was serious.

Infections leading to withdrawal from the study were also uncommon. There were two: One was the patient with pneumonia that I just described; the other was a non-serious cutaneous infection.

In addition to the pivotal study, we have an open-label extension study in which patients who have completed the trial that I just described are eligible to receive up to three years of additional therapy. We enrolled 181 subjects in this trial, and to date, 160 subjects have completed one additional year of therapy, and 75 subjects have completed two additional years of therapy.

We've not reached a pre-specified analysis point for this study; however, I've summarized briefly some adverse event experience here. To date, three subjects

have reported serious adverse experiences. One was a linked event of abdominal tenderness, dehydration, and pregnancy. This pregnancy ended in an elective termination.

The second was a subject with a prior history of anxiety who reported an SAE of anxiety during the trial. The third was a subject who had a post-operative bowel obstruction following elective repair of a congenital ureteral abnormality, and that surgery required an abdominal incision.

I'd now like to discuss the broader etanercept safety experience, again with a particular emphasis on the use of this agent in children. Outside of pediatric psoriasis, our pediatric clinical trials experience comes largely from JRA, Juvenile Rheumatoid Arthritis.

There are three studies that I'll discuss here. The first is our pivotal study in JRA. The second is an open-label extension study where patients could receive

up to 10 years of additional therapy. We currently have nine-year data reported.

And the third is a prospective cohort study looking at the use of methotrexate, etanercept, or the combination of these agents.

Of these three studies, the only one that reported non-serious events was the pivotal JRA study. Here, I've shown the most common infectious terms reported in that study. And I think you can see that the terms reported were very consistent with what was observed in the pediatric psoriasis study, and also consistent with what would be expected in a pediatric population.

If we now look at serious infections, the majority of our data come from the 10-year open-label extension. Again, we have nine-year data reported to date. Here, I'll call your attention to the fact that serious infections occurred uncommonly. The Y axis shows events per 100

patient-years. We've also given you the number of events shown in the little "n" above each bar. And as you can see, both the rates and overall number of events are small. There's no evidence for increased risk over time; however, there is an important caveat that we obviously have very few events reported between years 5 and 9 of the study.

If we look at infections in our three-year JRA cohort study, we see again that serious infections are relatively uncommon, and results were generally similar between groups.

I'd now like to describe to you our post-marketing experience. Again, with an emphasis on children. This pie graph shows the distribution of reports in pediatric patients by disease state. Not surprisingly, the majority of reports come from JRA, which is the only approved use of etanercept in children. I will call your attention to the fact that approximately 15 percent of our

reports come from the combination of psoriasis and psoriatic arthritis, which are shown in blue.

If we look at the distribution of reports across important organ system classes and compare the experience in adults and children, we see the following: here, we show adult reports in pink, pediatric reports in blue, and the distribution reports by important organ system classes is shown here. And as you can see, that matches quite comparably between adults and children across all organ systems.

The most frequent reported terms fall under the category of general and administration site. Most of these are injection site reactions. If we look at infections and infestations, the majority of reports are very consistent with the patterns that I described to you previously. And the most commonly reported terms are consistent with what would be expected in an ambulatory

pediatric population.

If we now look at pediatric post-marketing reports of infection with fatal outcome, we find 16 reports. I'll call your attention to a couple of features of the data. First, a number of these occurred in patients with systemic illness, including systemic onset JRA. And in addition, a number occurred in high-risk settings, such as bone marrow transplantation.

In addition, the majority of these subjects reported concomitant immunosuppressive therapy. Twelve of 16 reported these therapies, and 9 reported use of multiple agents. The use of combination immunosuppressive therapy would be very unlikely in a pediatric psoriasis population.

In addition to the four who reported no concomitant immunosuppressive meds, two were in high-risk settings, GVHD, Graft Versus Host Disease.

And although we have no