DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

and

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Monday, July 12, 2004

8:00 a.m.

ACS Conference Room
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

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Jonica Bull, M.D.
Denise Cook, M.D.
Tapash Ghosh, Ph.D.
Shiowjen Lee, Ph.D.
Jill Lindstrom, M.D.
Marilyn Pitts, Pharm.D.
Anne Trontell, M.D., MPH
Jonathan Wilkin, M.D.
Jiaqin Yao, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. STERN: Good morning, everyone. I'm Robert Stern, the Chairman of the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting. And today we're here to consider the application of oral tazarotene capsules for the treatment of moderate to severe psoriasis, including risk-management options to prevent fetal exposure.

I'd like to start the meeting by welcoming everyone, and then beginning directly across with me--if everyone would introduce themselves in terms of their role at this meeting.

DR. HONEIN: I'm Peggy Honein. I'm an epidemiologist with the CDC's Birth Defects group. And I'm here as part of Drug Safety Committee.

DR. FURBERG: I'm Curt Furberg at Wake Forest University. I'm a member of the Drug Safety and Risk Management Advisory Committee.

DR. KATZ: Robert Katz. I'm a dermatologist in private practice. Im a member of the Drug Advisory Committee.

DR. KNUDSON: I'm Paul Knudson. I'm the Consumer Representative on the Dermatology Advisory Committee.

DR. SELLERS: I'm Sarah Sellers. I'm a pharmacist and a drug-safety expert.

DR. SCHMIDT: I'm Jimmy Schmidt, private practice in Houston, and I'm on the committee.

DR. RAIMER: Sharon Raimer, University of Texas, Galveston. I'm on the Dermatology Committee.

DR. EPPS: Roselyn Epps, Chief of dermatology, Children's National Medical Center, and member of the Dermatology Advisory Committee.

MS. SHAPIRO: Robyn Shapiro, Director of the Bioethics Center at the Medical College of Wisconsin, and I'm on the Drug Safety Committee.

DR. RINGEL: Eileen Ringel. I'm on the Dermatological Advisory Committee. I'm a dermatologist in private practice in Waterville, Maine.

DR. STERN: And, again, I'm Rob Stern. I'm a dermatologist from Boston.

MS. TOPPER: I'm Kimberly Topper. I'm the Executive Secretary for this committee.

DR. GARDNER: Jacqueline Gardner, University of Washington School of Pharmacy, on the Drug Safety Committee.

DR. WILKERSON: Michael Wilkerson, dermatologist and member of the DODAC committee.

DR. DAY: Ruth Day, Duke University. I direct the medical cognition lab there, and a member of the Drug Safety Committee.

DR. TRONTELL: Anne Trontell, Deputy Director of the Office of Drug Safety in the Center of Drugs at FDA.

DR. COOK: Denise Cook, I'm a Medical Office in the Division of Dermatologic and Dental Drug Products.

DR. WILKIN: Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products, Center for Drugs.

DR. BULL: Good morning--Jonica Bull, the Director of the Office of Drug Evaluation V.

DR. STERN: Thank you very much.

We'll now begin with Dr. Bull giving some introductory--oh, we'll, now begin with conflict of interest, from the person at my right, Ms. Topper.

Conflict of Interest Statement

MS. TOPPER: Thank you.

The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made as part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting, all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have bee granted to the following participants: Dr. Michael Wilkerson, for his speakers bureau activities for a competing firm, which he receives less than $5,001 per year; Dr.

Curt Furberg, for his unrelated consulting for a competing firm, which he receives less than $10,001 per year; Dr. Stern, for his unrelated consulting for three competing firms, for which he receives less than $10,001 per year, and from one firm, and between $10,001 and $50,000 per year from the other two firms; Dr. Ruth Day, for her unrelated consulting for a competing firm, for which she has greater than $50,000 pending.

In accordance with 21 U.S.C. 355(n)(4), an amendment of the section of 505 of the Food and Drug Modernization Act, waivers have been granted for the following participants: Dr. Sharon Raimer owns stock in two competing firms, worth between $5,001 and $25,000 each; Dr. Sarah Sellers owns stock in a competing firm worth between $5,001 and $25,000. Because these stock interests fall below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

A copy of the waiver statements may be obtained by submitting a written request to the

agency's freedom of information office, Room 12A-30 of the Parklawn Building.

There will be no industry representative at today's meeting. As you may be aware, the FDA has appointed industry representatives who currently serve on each of these committees, but both appointed industry representatives work with the sponsors that are directly affected by the matter before the joint committee.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firms they may wish to comment upon.

Thank you.

DR. STERN: Thank you very much.

Dr. Bull?

Welcome and Introduction

DR. BULL: Welcome. Our thanks to all of you present who have taken time to be with us this morning. Our thanks must include an acknowledgment of the time the Advisory Committee members have spent reviewing the background materials provided.

I would also like to extend my thanks to an extraordinary group of scientists in the Center for Drug Evaluation and Research, from the Division of Dermatologic Drugs, the Office of Biostatistics, the Office of Biopharmaceutics, who will be presenting to you this morning. As well, I would also like to acknowledge the work of the project manager in the Division of Dermatologic Drugs, Khalyani Bhatt, as well as a standing team from the Executive Operations Office of Advisors and Consultants, Ms. Kimberly Topper and Ms. Shalini Jain.

The purpose of an advisory committee meeting is to provide expert scientific advice and recommendations to the agency regarding clinical investigations and proposed marketing approval for

a drug product. Our focus for today's deliberation is an application for oral tazarotene for the treatment of moderate to severe psoriasis, including risk management options to prevent fetal exposure.

The mission of the Center for Drug Evaluation and Research is to assure that safe and effective drugs are available to the American people. This means that we thoroughly assess the adequacy of the clinical trial design and endpoints for a proposed treatment--in this instance that of psoriasis, as well as the adequacy of the trial outcomes in support of the product's efficacy, safety, and its overall risk-to-benefit.

This committee deliberated earlier this year on another drug in this class of products, and the continuing challenges faced in risk management to ensure safe use and the optimal minimization of adverse events, especially those related to fetal exposure during a course of treatment. Our hope is that the background materials and presentations provided by the FDA and by Allergan will assist you

in responding to the agency questions, and provide for a thorough and independent deliberation of the important issues at hand.

We look forward to a productive and informative day.

Thank you.

DR. STERN: Thank you.

Now, Dr. Wilkin will speak to us.

Introduction and Overview of the Topic

DR. WILKIN: Psoriasis is a very common disorder. It's a chronic disorder, and it's a very costly disorder, in terms of both monetary expenses, and also in terms of the quality of life of those patients who have psoriasis.

We'll have two speakers this morning: one representing industry--Dr. Menter--and one from FDA, Dr. Cook--who will describe the current landscape available to dermatologists--the current products in the armamentarium for psoriasis.

I think one of the pieces that will become apparent is that there is no perfect drug. There are products which have definite side effects;

other products which are very new, and we're still going to be learning about their side effects. No product has perfect efficacy.

And so this is the background against which, I think, the committee needs to deliberate in their recommendations for the particular product today.

We do have a major focus on the risk-management program to prevent fetal exposure, but we must not lose sight that we're also thinking about the overall balance between benefit and risk for this product.

Thank you.

DR. STERN: Thank you very much.

And now Dr. Cook will talk to us a bit about psoriasis.

Introduction to Psoriasis and the State of the Armamentarium

DR. COOK:[Off mike.] [Inaudible.]

Sorry--can you hear me now?

We thought it appropriate, since people were from varying backgrounds, to give a review on

psoriasis. I apologize for those who are well-versed in the disease process.

[Slide.]

Psoriasis is a polygenic disease, and varying triggering factors--for example, trauma, infections or medications may elicit a psoriatic phenotype in predisposed individuals.

Today, I'm going to speak on the prevalence of psoriasis, the genetics and pathogenesis; the clinical variants of psoriasis, and the state of the armamentarium as it exists today.

[Slide.]

Psoriasis occurs in approximately 2 percent of the world's population. The prevalence in the United States may be as high as 4.6 percent. Its highest incidence occurs in Caucasians. In Africans, African Americans and Asians, the incidence of psoriasis is somewhere between 0.4 and 0.7 percent.

[Slide.]

There is an equal frequency in males and

females. It occurs in a one-to-one ratio. It may occur at any age from infancy to the 10th decade of life.

The first signs of psoriasis occurs in females at a mean age of about 27 years, and in males at 29 years.

[Slide.]

There are two general peaks of occurrence: one at age 20 to 30 years, and one between 50 and 60 years.

Psoriasis in children is very low. The incidence is between 0.5 and 1.1 percent in children 16 years and younger, and the man age of onset--when it does occur in children--is between 8 and 12.5 years.

[Slide.]

Two-thirds of patients who have the disease have mild disease. One-third of patients have moderate to severe disease.

Early onset--which is usually prior to age 15--is associated with more severe disease, and these patients are more likely to have a positive

family history.

As mentioned earlier, this is a life-long disease. The remitting and relapsing of the disease entity is unpredictable. There have been spontaneous remissions of up to five years reported in approximately 5 percent of patients who suffer from psoriasis.

[Slide.]

The genetics and pathogenesis of psoriasis: there's a lot of information that psoriasis is linked to the immune system, and that the major histocompatibility complex where psoriasis has been shown is on the short arm of chromosome 6. It's also linked to many histocompatibility antigens; the most common, and the one with the highest risk of family history, is HLA-Cw6. Other HLA antigens associated with psoriasis include HLA-B13, -B17, -B37 and B216.

It's also felt that psoriasis may have a t-lymphocyte-mediated mechanism associated with its pathogenesis.

[Slide.]

Psoriasis is not just confined to the skin, and there is evidence that this is a system disease, and that it's from the Koebner Phenomenon, which happens on normal skin, where patients may have trauma, and then the lesions of psoriasis appear. Patients also have been show to have an elevated erythrocyte sedimentation rate; increased uric acid levels may lead to gout; patients may have mild anemia; elevated à 2-macroglobulin; they may have elevated IgA levels; and they may also have increased quantities of immune complexes.

[Slide.]

Psoriasis also may be associated with arthropathy, and there is also an aggravation of psoriasis by systemic facts--as I mentioned at the beginning of the talk--and that could include medications, focal infections, stress.

Psoriasis also comes in the form of life-threatening disease. And there are two variants of that that I'm going to speak about later: erythrodermic psoriasis, and pustular psoriasis.

Now I'm going to speak about the clinical variants of psoriasis.

[Slide.]

The characteristic lesion of psoriasis is a sharply demarcated erythematous plaque with micaceous silvery white scale. This is supported histopathologically by a thickening of the epidermis; tortuous and dilated blood vessels; and an inflammatory infiltrate, primarily of lymphocytes.

[Slide.]

And here, from Bolognia--where all the pictures that you're going to see--clinical pictures that you're going to see--is from this textbook of dermatology by Bolognia--and here we have an erythematous plaque. You can see the outline of the erythema; the elevation of the plaque above the skin surface, and the thick micaceous, silvery scale.

[Slide.]

The severity of the disease is usually characterized by three cardinal signs of psoriasis:

plaque elevation, erythema and scale. Body surface area also plays a part. Patients are very concerned about how much of their skin surface is covered by the disease. But in determining severity, it could be very complex, because different people see body surface area differently.

[Slide.]

The most common variant of psoriasis is the chronic plaque psoriasis. The plaques may be as large as 20 cm; psoriasis is usually a symmetrical disease. The sites of predilection can include the elbows, the knees, the presacrum, scalp, the hands and the feet.

[Slide.]

I'm going to show you some pictures now of chronic plaque psoriasis. Here you can see that the disease is very symmetrical, and can involve a decent part of the body surface area.

[Slide.]

This is a picture of psoriasis of the feet.

[Slide.]

Now, chronic plaque psoriasis may be widespread. It can cover up to 90 percent of the body surface area. The genitalia can be involved in up to 30 percent of patients. Most patients also have nail changes which include nail pitting and "oil spots." And sometimes the involvement of the nail bed is very severe, with onychodystrophy and loss of the nail plate.

[Slide.]

Here is a picture of widespread chronic psoriasis. And I think all of us would agree that this is probably a severe case of psoriasis.

[Slide.]

This is a picture of the genitalia with psoriasis.

[Slide.]

Here is a picture of psoriasis of the nail, with nail pitting and oil spot, where the nail is--the nail plate is being separated from the nail bed.

[Slide.]

And some more severe form of nail

psoriasis, with, again, oil spots, onychodystrophy, and loss of the nail plate.

[Slide.]

Symptoms of psoriasis include pruritus, pain. Patients who have widespread psoriasis sometimes complain of excessive heat loss. Also, patients hate the way the disease looks; sometimes have low self-esteem, have feelings of being socially outcast and really dislike the excessive scaling.

[Slide.]

The next variant of psoriasis that I'm going to speak about is guttate psoriasis. It's characterized by numerous 0.5 to 1.5 cm papules and plaques; usually has an early age of onset. It's the most common form in children, often triggered by streptococcal throat infection.

In children, the remissions may be spontaneous. In adults it's often chronic.

[Slide.]

Here is a clinical presentation of guttate psoriasis, with the small papules, and plaque here.

And this is a picture of someone who had an eruption of guttate psoriasis after a sunburn.

[Slide.]

The life-threatening forms of psoriasis are generalized pustular psoriasis and erythrodermic psoriasis.

[Slide.]

Generalized pustular psoriasis is an unusual manifestation of the disease. It can have a gradual or an acute onset. It is characterized by waves of pustules on erythematous skin after short episodes of fever, from 39 to 40 degrees centigrade. Patients may have weight loss, muscle weakness, hypocalcemia, leukocytosis and an elevated ESR.

[Slide.]

The cause is obscure, but we do know that there are several triggering factors, and they include: infection, pregnancy, lithium, hypocalcemia secondary to hypoalbuminemia; irritant contact dermatitis, and withdrawal of gluccocorticosteroids, primarily systemic.

[Slide.]

And here is a clinical presentation of pustular psoriasis. And you can see the erythema, with the pustules scattered about.

[Slide.]

Erythrodermic psoriasis--in this disease, which is also a life-threatening form of psoriasis, the classic lesion of psoriasis is lost. The entire skin surface becomes markedly erythematous, with desquamative scaling. Often the only clues to the underlying psoriasis are the nail changes, and usually there's facial sparing in erythrodermic psoriasis.

[Slide.]

Triggering factors may include systemic infection, withdrawal of high potency topical or oral steroids; withdrawal of methotrexate; phototoxicity, and irritant contact dermatitis.

[Slide.]

Here is the clinical presentation of erythrodermic psoriasis in a patient after withdrawal of methotrexate.

[Slide.]

Now, I'm going to speak of the state of the armamentarium of psoriasis. We're mainly going to focus on moderate to severe psoriasis, since that's the topic of the drug product under consideration for today.

There is a wide range of therapies for moderate to severe psoriasis. None induce a permanent remission, and all have side effect that can place limit on their use, and usually require that patients are treated in a cyclical fashion.

[Slide.]

These therapies include topical corticosteroids, topical vitamin D3 analogues, topical retinoids, photochemotherapy, and systemic therapies which may be oral or parenteral.

[Slide.]

Topical corticosteroids that are usually used in moderate to severe psoriasis are those of the high potency and super potent topical steroids. These include the fluocinonide family, betamethasone dipropionate cream, the clobetasol

priopionate family, diflorasone diacetate ointment, and betamethasone dipropionate ointment.

[Slide.]

The side effects associated with use of these drugs include skin atophy, burning and stinging; and, systemically, suppression of the hypothalamic-pituitary-adrenal axis. This may occur after two weeks use with certain topical corticosteroids. Usually those are the super potent type.

[Slide.]

Topical vitamin D 3 analogues--the prototype for this group is calcipotriene. There are three formulations: cream, ointment and scalp solution. The former two are approved for plaque psoriasis, the latter for moderate to severe psoriasis of the scalp.

[Slide.]

Side effects for topical vitamin D3 analogues are primarily cutaneous, and include burning, stinging, pruritus, skin irritation and tingling of the skin.

[Slide.]

The topical retinoids that are approved for the treatment of plaque psoriasis are tazarotene gel and cream. They are available in two strengths: 0.05 percent, and 0.1 percent.

The side effects include pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, skin pain. And there have been cases of hypertriglyceridemia.

[Slide.]

Additional indicatiosn for topical tazarotene in the 0.1 percent gel is approved for the treatment of facial acne vulgaris of mild to moderate severity. And the 0.1 percent cream is also approved as an adjunctive agent for use in the migitation of facial fine wrinkling, facial mottled hyper-and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.

[Slide.]

Topical tazarotene--both products are pregnancy category X. They are contraindicated in

women who are or may become pregnant. And there are some requirements before and during therapy. These include a negative pregnancy test two weeks prior to initiation of therapy. Therapy must be initiated during a normal menses. And women of childbearing potential should us adequate birth control.

[Slide.]

Now I'm going to speak on photogemotherapy. There are two types of phototherapy for the treatment of moderate to severe psoriasisThese include ultraviolet B, or UVB; and ultraviolet A plus psoralen, more commonly known as PUVA.

[Slide.]

There are two types of UVB: broadband UBV and narrowband UVB. The treatment is time consuming. Patients usually must come two to three visits per week for several months. And the side effect is possibility of experiencing an acute sunburn reaction.

[Slide.]

PUVA consists of ingestion of or topical treatment with a psoralen followed by UVA. It is usually reserved for severe, recalcitrant, disabling psoriasis. This form of treatment for psoriasis is also time-consuming. It usually requires two to three visits per wekk, and at least six weeks of treatment to get clerance.

There are several precautions that must be taken for patients who are treated with PUVA. Patients must be protected from further UV light for 24 hours post treatment. And with oral psoralen, they must have wrap-around UV-blocking glasses for 24 hours post treatment.

[Slide.]

Side effects with oral psoralen include nausea, dizziness and headache. Early side effects with PUVA are pruritus, but late side effects include skin damage, and the increased risk for skin cancer, particularly squamous cell skin cancer; and after maybe 200 to 250 treatments--which is really a long time--patients may be at increased risk for melanoma.

[Slide.]

Contraindications to PUVA include patients less than 12 years of age; patients with a history of light sensitive disease states; patients with, or with a history of melanoma; patients with invasive squamous cell carcinoma; and patients with aphakia.

[Slide.]

Now, the system therapies--these come in two types: oral and parenteral. The oral therapies are methotrexate, Neoral--or cyclosporine--and Soriatane--acetretin. The parenteral therapy includes, most recently approved biologics which are Amevive, Raptiva and Enbrel. And I will speak--as a prototype--on Amevive, which was first approved.

Methotrexate is a folic acid antagonist, usually reserved for severe, recalcitrant, disabling psoriasis. Maximum improvement can be expected after eight to 12 weeks.

[Slide.]

The contraindications for methotrexate

include nursing mothers, patients with alcoholism, alcoholic liver disease, patients with other chronic liver disease; patients with overt or laboratory evidence of immunodeficiency syndromes, and patients who have preexisting blood dyscrasias.

[Slide.]

This drug product is also a Category X. It's contraindicated in pregnant women with psoriasis, and pregnancy must be excluded in women of childbearing potential, and pregnancy should be avoided if either partner is receiving methotrexate during and for a minimum of three months after therapy for male patients and for at least one ovulatory cycle after therapy for female patients.

[Slide.]

Side effects of methotrexate are numerous. They include acute or chronic hepatotoxicity, hepatic cirrhosis, leukopenia, thrombocytopenia, anemia, stomatitis, nausea/volmitting, alopecia, photosensitivity, burning of skin lesoins and, rarely, interstitial pneumonitis.

[Slide.]

Multiple screening tests are necessary before using methotrexate. There are also recommendations for hepatic monitoring, which include period liver function tests, including serum albumin--although, I must say, liver function tests are not a good screen with methotrexate for hepatic damage. Therefore, there are recommendations for liver biopsy which include doing it pretherapy or shortly thereafter, also after a cumulative dose of 1.5 grams, and after each additional 1 to 1.5 grams of use.

[Slide.]

Neoral, or cyclosporine, is a potent immunosuppressive. It is approved for adults that are non-immunocompromised, with severe, recalcitrant plaque psoriasis. Maximum efficacy is achieved after about 16 weeks of therapy.

There are contraindications for use of this drug, which include concomitant PUVA or UVB therapy; using methotrexate or other immunosuppressive agents; using coal tar or radiation therapy. Patients with abnormal renal

function; patients with uncontrolled hypertension; patients with malignancies and nursing mothers cannot use this drug.

[Slide.]

There are many side effects for Neoral. The highest ones are the possibility of irreversible renal and onset of hypertension; then headache, hypertriglyceridemia, hirsutism, pareshesias, incluenza-like symptoms, nausea, vomiting, diarrhea, lethary and arthralgia.

[Slide.]

Multiple screening tests--prescreening tests--are needed for use of Neoral. And the tests must continue throughout treatment, with dosage adjustment as necessary to prevent end-organ damage.

[Slide.]

Soriatane is the only oral retinoid that's approved for psoriasis, and it's approved for the treatment of severe psoriasis in adults. One can see significant improvement with therapy after eight weeks.

[Slide.]

Contraindications for use of Soriatane include patients with severely impaired liver or kidney function; patients with chronic abnormally elevated blood lipid values; patients who are taking methotrexate; and patients who use ethanol when on therapy and for two months following therapy in female patients.

[Slide.]

Soriatane is also a pregnancy Category X drug product as it is a human teratogen. It's contraindicated in pregnant females or those who intend to become pregnant during therapy or anytime up to three years post therapy.

[Slide.]

Side effects with Soriatane are those that are usually associated with oral retinoid therapy, and include chelitis, alopecia, skin peeling, dry skin, pruritus, rhinitis, xeropthlamia, and arthralgia.

[Slide.]

There are many laboratory abnormalities

also, and those include hypertriglyceridemia, decreased HDL, hypercholesterolemia, elevat3d liver function tests, elevated alkaline phosphatase, hyperglycemia and elevated CPK. However hepatitis and jaundice occurred in less that 1 percent of patients in the clnical trials on Soriatane.

[Slide.]

Multiple prescreening tests also must be used for Soriatane, and you must have continued monitoring throughout therapy, with possible dosage adjustment.

[Slide.]

The parenteral therapy, as I mentioned before, are lately on the scene. And the one I'm going to speak on is Amevive. It is an immunosuppressive dimeric fusion protein. It's made up of an extracellular CD2-binding portion of the human leukocyte function antigen-3, which is linked to the Fc portion of the human IgG1 molecule.

[Slide.]

Amevive is indicated for the treatment of

adult patients with moderate to severe chronic plaque psoriasis. With 12 weeks of therapy, a disease state of clear or almost clear was achieved by 11 percent of patients via the intravenous route, and 14 percent of patients via the intramuscular route.

[Slide.]

The side effects with Amevive include a dose-dependent reduction in circulating CD4 and CD8 T lymphocytes. Therefore this drug should not be administered to patients with low CD4 counts. CD4 counts must be monitored before and weekly throughout therapy.

[Slide.]

Side effects that have been associated thus far with Amevive have been lymphopenia. There's also been an increased risk of malignancies, particularly skin cancer--or basal cell carcinoma and squamous cell carcinoma--and an increased risk for lymphoma.

There have been serious infections requiring hospitalization. There is also a risk of

reactivation of chronic, latent infections, and of hypersensitivity reactions.

[Slide.]

hopefully this has given you a good background on the disease of psoriasis, and also the state of the armamentarium for treating this disease.

Thank you.

DR. STERN: Thank you very much for a very nice presentation.

Could I ask two quick questions?

The first is: topical tazarotene, the package labeling says that there should be a pre-treatment pregnancy test in women who might be or become pregnant. Is that the labeling for topical tazarotene?

DR. COOK: Yes, what I had up there, it's directly out of the label.

DR. STERN: Okay. And the second is: you had, for acitretin that the indication is severe psoriasis, not moderate to severe psoriasis.

DR. COOK: Yes, severe--

DR. STERN: It's severe.

DR. COOK: It's severe psoriasis.

DR. STERN: Okay. Thank you very much. Thank you for a great presentation. It was very clear. And I enjoyed it.

And now we will go on to the Allergan presentation, with Dr. Patricia Walker, Vice President of the Skin Care Pharmaceuticals Division, giving the introduction for the sponsor's application.

Allergan NDA Presentation

Introduction

DR. WALKER: Good morning.

Allergan is here today to seek approval for our oral tazarotene gel formulation--gel capsule formulation--for the treatment of moderate to very severe psoriasis.

What I'd like to show you today is that tazarotene is a retinoid, and as a retinoid, it does have some unique pharmacology and receptor activity. We've demonstrated efficacy in the treatment of moderate to very severe psoriasis. We

feel our drug is differentiated from other retinoids--and actually has an improved safety profile relative to other drugs in this class. Tazarotene is a teratogen--or a probable teratogen--and we've developed a Risk Minimization Action Plan around this.

[Slide.]

It is available in a topical formulation, as you heard this morning from Dr. Cook. The gel formulation was approved in 1997 for the treatment of psoriasis, and for acne at that time. A cream formulation was approved in 2000 for the treatment of psoriasis; 2001 for the treatment of acne; and then, later for the treatment of photodamage, or signs and symptoms of photoaging.

At the time of the psoriasis cream approval, we developed and worked with the Derma-Dental Division to develop a new scoring system, which we refer to as the "overall lesional assessment. Later in the morning, in my talk, I'll go over that assessment.

We started the oral tazarotene formulation

development in 1998, with Phase 2 studies. We initiated the Phase 3 studies in 2001, and we filed the NDA last November, in 2003.

Just to set the stage, we've studied many patients with this drug. WE have nearly 1,700 patients studied with oral tazarotene, 901 of which have been treated with at least 4.5 mg or higher.

[Slide.]

The introduction is from me, then you're going to hear from Dr. Alan Menter, who's going to give you a brief overview of the disease, and what the unmet need is, and the treatment options.

I'll come back and share with you some of the pharmacology of tazarotene; what the clinical development's been; and our proposed risk minimization action program.

And then Dr. Menter will wrap up with a risk benefit assessment.

[Slide.]

Available to answer questions today are several of my colleagues from Allergan in various disciplines--

[Slide.]

--as well as some consultants who have worked with us extensively on analyzing and looking at our data.

At this time, I'd like to turn the podium over to Dr. Menter to give you the disease overview and treatment options.

Psoriasis: Disease Overview and Treatment Options

DR. MENTER: Thank you, Dr. Walker--Mr. Chairman, colleagues, patients, ladies and gentlemen.

My name is Alan Menter, and I'm a clinician, practicing dermatologist in Dallas, Texas. From a conflict of interest conflict of interest point of view, I have consulted with Allergan, and have been involved in clinical research with Allergan, with oral tazarotene, as well as with multiple other drugs related to psoriasis. I do not own any stock in Allergan corporation.

[Slide.]

As we've so eloquently heard this morning

from Dr. Cook, psoriasis is a common disease. It is probably one of what we consider the autoimmune diseases in all medical conditions. And I'm not going to reiterate some of the things that Dr. Cook mentioned in her excellent review, but just merely highlight a few issues that I believe are important when considering systemic therapy for psoriasis patients.

[Slide.]

The prevalence, as she has mentioned, is equal in male and females. And I think this is an important issue when we come to talk about patients who are candidates for systemic therapy, because I believe at this stage, a number of patients--particularly young females of child-bearing potential--are currently excluded from systemic therapy because of pregnancy issues.

And, as she mentioned, there are multiple genes associated with psoriasis. And I think also of importance is the fact that psoriasis is linked, as a systemic disease, with other immune-mediated, or autoimmune disease such as diabetes, lupus,

Crohn's--and there have been many genetic linkages found in which psoriasis patients have other diseases like diabetes, lupus and Crohn's disease.

We all recognize that psoriasis is a condition that patients struggle with. And, as Dr. Wilkins said, quality of life--that I'd like to stress--is a major issue. This is not just a physical problem that patients have to put up with, they have to bear the emotional struggle that comes with facing themselves on a day-to-day basis, their loved ones, their peers, on a day-to-day basis with this condition we call psoriasis; and itching, and pain, and disfigurement are common. And patients will tell you about the problems they have relating to dealing with the day-to-day manifestations of psoriasis.

[Slide.]

From a point of view of pathogenesis, I think we don't recognize--as Dr. Wilkin also said, and Dr. Cook mentioned--that psoriasis has to be considered not a skin disease. This is a systemic disease. And I think for too long we, as

clinicians, have really overlooked the systemic nature of psoriasis. It is certainly a disease that is driven by the immune system, by T cell proliferations, the release of various cytokines--chemicals that then induced this hyperproliferation and the scale that we see inherent in patients with psoriasis.

So I do believe that we must no longer look at psoriasis as a pure skin disease; look at it as a systemic disease like we do other immune-mediated systemic diseases, like I mentioned.

[Slide.]

It's a diverse disease. Eery patient with psoriasis looks different. For those of us in clinical practice who see psoriasis on a day-to-day basis, psoriasis patients may, at first glance, look similar. But there are nuances, there are differences in expression of the disease. And even within one individual patient, their disease may change from discoid psoriasis, as Dr. Cook showed, to pustular psoriasis, to erythrodermic psoriasis,

and back again to ordinary psoriasis.

[Slide.]

She showed pictures of genital involvement. This leads to massive issues in interpersonal relationships. And no longer can we consider genital involvement, scalp involvement, as mere nuisance issues. These are issues that really do involve patients' interpersonal relationships, at work and at home, on a day-to-day basis. And we have to take cognizance of the fact that psoriasis has a major burden on the quality of life. And for those patients in the audience today, Im sure they could tell you the issues that they deal with on a day-to-day basis related to quality of life. It's not just physical functioning, but the mental functioning as well.

And I think when we consider retinoids, it's interesting to note that there are retinoids for non-dermatologic conditions, like leukemia and cutaneous lymphoma. And psoriasis rarely has been shown, in all aspects of quality of life, to impact negatively, equally, if not worse, the mental and

physical aspects of a patient's life, with cancer patients, arthritis patients, and diabetes patients. So, again, stressing the quality of life issues that are inherent in this.

And I've mentioned interpersonal relationships, and I've mentioned work disability as well.

And, as Dr. Wilkin says, this is a costly disease, and it's not getting any cheaper as new drugs become available to us. But I do not believe we need to take a backseat to colleagues in other areas of medicine who have expensive drugs available to them to treat diseases like arthritis and Crohn's disease.

[Slide.]

If one takes patients with various areas of psoriasis--palmar/plantar psoriasis--a patient who's--which is a fairly common area of involvement--patients struggle with locations on the palms, even though this may only affect a small proportion of the body. Patients--who you can see here--with palms and soles do not get by with

creams and ointments. They frequently need systemic therapy to control their disease. So, body surface area by itself should not be used as a pure parameter for indication of systemic disease.

And the treatment has to be considered asa life-long treatment. Psoriasis patients--as has been mentioned by Dr. Cook and myself--patients start early in life with psoriasis. The vast majority of patients present before the age of 36. So, for those of them who life a long life, basically, they have to deal with this for the next 50, 60 years of their life. And treatment has to be tailored accordingly. You cannot treat psoriasis for three weeks, for three months, for six months or for one year. Treatment is a life-long treatment. And no cures are currently present at the current time.

[Slide.]

So where are we with psoriasis therapies? It's probably true to say that psoriasis is a very under-treated disease, and there are various reasons for this.

If we look at the figures--that has been mentioned by Dr. Cook and myself--of approximately 10 to 25 percent of patients; in the United States, that means a minimum of 450,000 patients have moderate to severe disease. Currently, only about 125,000 of those patients are being treated with systemic therapy. So, hence, there are two-thirds of the patients with moderate to severe psoriasis are not being treated. And the question is: why?

And I think the reasons are shown here. There are safety concerns with the drugs. It's time-consuming to put up with the day-to-day issues relating to these drugs. There's monitoring involved in psoriasis; and, obviously the cost issue, as well.

[Slide.]

So, I'm not going to review the side-effect profile. All these drugs work well. And I think we have to recognize that we're not here to knock any individual product. We have great drugs. We've had methotrexate available for 30 years. We've had retinoids available for nearly

20 years. The biologic drugs are new. But all of these drugs have issues relating to them that make for monitoring and make for difficulty in day-to-day management of these patients.

[Slide.]

So, basically, in summary: psoriasis is not a single disease. It is a very diverse disease. It is a disease that has major problems and quality of life issues.

And the other aspect we have to recognize is that as patients age, they develop co-morbid conditions. They develop liver problems which precludes them from certain therapies such as methotrexate. They may have compromised renal function which precludes cyclosporine. And all day--and my colleagues--my dermatology colleagues in the audience--are faced with making choices of drug therapies for patients who have co-morbid conditions that will preclude certain drugs. So we definitely need a full range of treatment.

And I do believe that it is important for our psoriasis population that we have--as we do

have in other systemic diseases--a full range, and comprehensive range of medications so that we can choose, in conjunction with our patients, the correct therapy for our patients.

Thank you.

DR. STERN: Thank you very much.

Oral Tazarotene - Pharmacology, Clinical Development, Risk Minimization Plan

DR. WALKER: I'm now going to share with you the pharmacology of tazarotene, and what we think makes it unique; the clinical development program; and the risk minimization plan that we are proposing.

[Slide.]

Just to summarize the data that we have for tazarotene as a molecule, it is a prodrug. It actually has only one active metabolite, and that's tazarotenic acid. It's what's known as a third-generation retinoid, or acetylenic retinoid. It's a locked molecule, which prevents isomerization and non-specific binding, and it's a receptor-selective molecule.

[Slide.]

As already mentioned, retinoids have been on the market for a long time--both natural and synthetic forms--for over 20 years. These are very well known to dermatologists, but they're also used outside of dermatology. There's isotretinoin, altrans retinoic acid, etretinate--which has now been replaced by acitretin-- and bexarotene.

Retinoids are known to be essential for normal epithelial proliferation, differentiation, and embryo-fetal development.

There are two types of retinoid receptors that retinoids act through: the RAR receptors and the RXR receptors. These receptors always occur as a dimer. They can occur as either a hetero-dimer, with the RAR binding with an RXR, or as a homo-dimer, RXR-RXR receptors.

[Slide.]

There are also subtypes of these receptors. The receptor combinations and subtypes are important because there are different side effects noted--and different biological effects

noted--with each subtype. And there's also tissue-specific receptor expression.

[Slide.]

The current retinoid therapies used in dermatology--primarily acitretin and isotretinoin--are what are known as pan-agonists. Acitretin is a pan-agonist for all three subtypes of the RAR receptor. Isotretinoin and its metabolites are pan-agonists for the three subtypes of the RAR receptor, as well as the RXR receptor.

This is important because activation of these subtypes are related to many of the side effects that we heard about this morning from Dr. Cook, such as hyperlipidemia, hepatotoxicity, epistaxis, eye irritation and dryness--those side effects are specifically associated with the RARà subtype, as well as the RXR-receptor subtypes.

[Slide.]

This is a distinction for tazarotene. Tazarotene is not a pan-agonist. Tazarotene has specific receptor activation at á, to a much higher level than at the RARà. There is no

activity at the RXR receptor.

This is important for treating skin disease because skin disease specifically has a receptor RAR in karotinocytes.

[Slide.]

It's a locked molecule. And the locked molecule--if I can try to use the pointer here--the locked molecule here is due to the triple bond there. That prevents this molecule from flopping around and giving non-specific binding.

This receptor selectivity that I've described here we feel can enhance the therapeutic effect--can enhance that effect by really minimizing side effects that are unwanted, and thus improve the safety profile.

[Slide.]

I'm now going to go on and share with you the clinical development program.

We've done 12 Phase 1 studies in normal healthy volunteers; one Phase 2 study in patients with moderate to very severe plaque psoriasis, and four Phase 3 studies, patients with moderate to

very severe plaque psoriasis.

[Slide.]

Our clinical Phase 1 studies in normal healthy volunteers demonstrated that tazarotene could be given as a single daily dose for all patients. The dosing is not affected by the patient's body weight, and not affected by whether it's taken with or without food.

In in vitro studies, and some clinical studies, we've demonstrated that there are no expected drug-drug interactions. Tazarotene is metabolized by the P450 enzyme system, specifically CYP2C8 and the FMO.

The metabolism is not altered by alcohol ingestion. And tazarotene has a very short half-life of 7 to 12 hours.

[Slide.]

The efficacy data I'm going to share with you now is based on the Phase 2 dose-ranging trial, which is known as an 026P study; two Phase 3 pivotal trials, the 048P study, and the 049P. I'll try to remind you whether it's a pivotal trial, and

what the number is; or two Phase 3 open-label trials, which are the 050P and 052P.

[Slide.]

Tazarotene in the dose-ranging study--we determined that tazarotene 4.5 mg per day as a single dose would be an appropriate dose to take into our Phase 3 trial. These results were based on two stages of a dose escalation trial. The first stage went from zero--or placebo--up to 1.1 mg per day. Then we did dosing escalation cohorts; a 2.8 mg cohort together; a 4.2 mg cohort; and 6.3 mg.

We showed--and saw in the data, which I'm going to show you in just a moment--that there was really no clear dose response in doses ranging from .4 mg up to 2.8 mg. We did see a nice clinical response in the 4.2 and 6.3 mg dose groups.

[Slide.]

This is looking at the overal lesional assessment; looking at patients who achieved a "mild or less." I think you can see, with the kind of orange colored bar, or peach colored bar, that

mild disease really--there was not a clear dose response up to 2.8 mg, but you did see in the 4.2 and the 6.3 dosing groups that there was a nice response, with at least 80 percent of the patients achieving that "mild" disease.

Based upon these results, we chose the 4.5 mg dose to go into our Phase 3 trials.

[Slide.]

The Phase 3 trials looked at adult patients, 21 years of age or older, with stable plaque psoriasis on at last 10 percent of the their body surace area in an overall lesional assessment of at least 2, which was graded as a "moderate."

[Slide.]

So what is an "overall lesional assessment?" I did mention in our introduction that this measure was developed by Allergan, in collaboration with the FDA, back in 1997, for a cream development program. At that timethe FDA--the Division asked us to work on developing a scoring system which was clinically meaningful; a scoring system which was static--didn't require

physician memory; and one which didn't require physician's memory, was static, clinically meaningful, and used all the signs and symptoms of psoriasis.

So we worked and developed a scoring system that took all the major signs--plaque elevation, scaling, and erythema--they were on a six-point scale, from none to very severe disease. We used this in our cream development, and then have used this trial subsequently in our oral development. Physicians were trained on this scoring system using a photo-numeric guideline.

[Slide.]

An example of some of the photos from that guideline are shown on this slide. You can see, it's a "0"--again--to "5" scoring system, which is a six-point scale. "None" is no disease; "minimal" is disease with a little bit of erythema. It allowed a slight bit of scaling. A little more scaling and erythema with "mild" disease. You have a definite plaque at "moderate" disease, and then the plaque and scaling really increased to "very

severe disease."

[Slide.]

The primary efficacy variable in these trials were: patients had to enter with at least a moderate disease; moderate, severe or very severe disease. And to be considered a clinical success, those patients had to reach a score of "none" or "minimal." And that was the primary variable that we looked at. This is a very stringent criteria. So patients had to come in with moderate to very severe, and they needed to be a "none" or "minimal" to be a clinical success.

[Slide.]

We looked at other measures also. We had a second co-primary variable, which was looking at patients who had at least a two-grade change in their overall lesional assessment. We looked at a physician global response to treatment. We looked at body surface area. And then we looked at each individual sign of psoriasis--erythema, plaque and scaling--and those were scored on a five-point scale.

We looked at target lesions to see if there were different lesions that responded or not to psoriasis [sic]. We looked at elbows, knees, scalp and trunk. And,again, we looked at hose in terms of the specific signs of plaque, erythema and scaling.

We looked at overall pruritus. We looked specifically at scalp psoriasis; quality of life indexes, as well as photographs.

[Slide.]

743 patients were evaluated in these efficacy trials. 743 got the drug at least 12 weeks. We also did longer-term studies; the 52 and 50P trial. There were 261 patients who got oral tazarotene at least 24 weeks; 153 for 48 weeks; and 101 patients for 52 weeks.

[Slide.]

In the Phase 3 pivotal trials--this is the 48 and 49P trials--the patients were randomized to received 4.5 mg of tazarotene per day, versus placebo, for 12 weeks. The visits were at weeks 1, 2, 4, 8 and 12. There was a post-treatment period

build into this trial--and, actually, all the trials I'm going to talk about--which was also 12 weeks, and the patients were evaluated at weeks 16, 20 and 24.

[Slide.]

The demographics of the pivotal trials--this is the 48, 49P trials--were that the average was around 47 years of age; there were 60 to 80 percent males in the trial. This is different than what the demographics of the disease are, but is actually very consistent with a systemic psoriasis trials.

The mean body surface area was quite high: approximately 30 percent across all groups. And the overall lesional assessment was 3.4--so somewhere between a moderate and severe disease.

[Slide.]

Now, this is showing you the results of the two pivotal studies, looking at the primary efficacy variable of "none" or "minimal disease." So this is this is that very stringent criteria.

The light blue bars on the bottom are the

placebo. The orange bars are the patients treated with tazarotene. They're the orange lines.

What I think you can note, first off, by just looking at this, the quick look is that the two trials--same exact trial, different sites, different patients--they very closely mimicked each other. And I think you'll appreciate, as I go through this data, that all the trials closely mimicked each other. It makes my job a lot easier when you don't have one trial that doesn't fit with the others. All the trials mimicked each other.

So now looking at the orange lines as they go up, you can see that at week 12, which is the primary time point, between 15 to 20 percent of the patients reached this efficacy level of "none" or "minimal disease."

What's also interesting is that you look at 16 weeks--which is the post-treatment period--that's the darker side of the graph--you can see that more patients in one trial--almost 25 percent of the patients--reached that criteria, and the other group stayed about the same.

If you look through the post-treatment period, you can see that the effect was relatively sustained throughout the 12-week post-treatment period. These results were statistically significant as early as eight weeks.

As I've mentioned many times, the criteria of "none" or "minimal disease" is a very stringent criteria for success. Does that mean that only 20 percent of the patients improved with the disease?

What I want to show you here is: no, that's 20 percent of the patients achieved that stringent criteria, but more patients actually did respond.

If you look at the two sides of the graph, there's the tazarotene treated side, and there's the placebo side. So it's tazarotene, placebo.

Patients entered the trial--predominantly moderate overall lesional assessment. The yellow bar are patients with severe psoriasis. The little red bar at the top are patients with very severe psoriasis. So this is the tazarotene group, at baseline.

After 12 weeks of therapy, you can see that the moderates are certainly decrease. The "severes" are decreased, and the "very severe" patients--although not many patients all improved--and that this response was maintained in the post-treatment period.

So where did these moderates and severes go? Well, they go into the mild, none or minimal caregories. And, again, this graph shows that that response is somewhat sustained through the treatment period.

If you look at placebo--well, your purple and yellow bars, at the quick glance, don't change much. And, certainly, your "very severe"--is the little skinny red bar at the top--don't change at all.

Body surface area--we did measure body surface area. This is--the overall lesional assessment is different than the POSI score. The POSI score is a derived score, which includes body surface area a part of the derivation of that score. With our scoring system, the overall

lesional assessment is separate from the body surface area.

[Slide.]

So here we show body surface area, and the number of patients who actually had at least a 10 percent decrease. You can see, at week 12, between 30 to 40 percent of the patients had a 10 percent decrease in their psoriasis. It peaks at weak 16--or four weeks off of treatment--and that effect is relatively sustained throughout the treatment period. And, again, is statistically significant compared to placebo.

[Slide.]

We also looked at the measure of physician global--response to global improvement. So this is the physician saying, "How much better did this patient get?"

What I have here is the dta divided by how many patients the physicians felt got at least 50 percent better, and 75. The hash marks are the total height of the bar; shows how many patients got at least 50 percent better. And you can see at

week 12, at leaste 54 percent of the patients got at least 50 percent better.

That was relatively sustained in the post-treatment period, with 43 percent of the patients getting better. I think you can see it is statistically significant compared to placebo.

If you use a little more stringent criteria of how many patients got at least 75 percent better--that's the solid bar--you can see that at week 12, 30 percent of the patients got at least 75 percent better, and that was sustained in the post-treatment phase of 30 percent maintaining that.

So, again, there's a very stringent criteria of "none" or "minimal disease," which is a very high bar--which we had approximately 20 percent of the patients achieve. But the majority of patients do achieve some response of at least 50 percent or more improvement.

[Slide.]

These are just some clinical photographs that show how the patients did in this trial. The

patient on the left is at baseline, and then his response at week 12.

[Slide.]

These are some target lesions--the elbow, on the top, and the knees on the bottom--at baseline, and then the response at week 12.

[Slide.]

Another target plaque and elbow at baseline, and then a really nice response, again, at week 12.

[Slide.]

We had two long-term studies: the 052P study and the 050P study. Although these were primarily safety studies, I think toshow you just one efficacy graph I think is helpful.

The 052P study was an extension study from the privotal trial. So the 048, 049P trial--patients who at 12 weeks either had worsening disease or stayed the same were allowed to enroll in an open-label trial.

Ninety-two patients enrolled that had already been treated with 12 weeks of tazarotene,

versus 220 that had been treated the first 12 weeks with placebo. They went into the six month trial: 12 weeks treatment with tazarotene for all patients, and then another 12 week follow up.

So what we see in this group is that you have a subset of patients who got 24 weeks of therapy with tazarotene.

In contrast, the open-label study--the 50P study--was a pure safety study. All patients got tazarotene, 4.5 mg. They were dose for 52 weeks, and then had a second 12 weeks post-treatment response.

[Slide.]

The demographics of this trial were very similar to the demographics I showed you for the two pivotal trials. The mean age was, again, around 47 years of age. The body surface area was close to 30 percent, and the overall lesional assessment score was close to 3.4.

[Slide.]

Now, this is a graph showing the primary efficacy variable of "none" or "minimal" disease.

If you look at the yellow line first, the yellow line are patients who were treated with placebo and then enrolled into this open-label trial. So they should respond like what we showed in the pivotal trial. And they do.

At week 12, approximatley 20 percent of those patients had reached the stringent criteria of none or minimal disease, and that was relatively maintained across the 12-week post-treatment period.

What's interesting here--and the reason I like to show this data--is that the orange line are patients who didn't respond to the first 12 weeks of therapy. And they didn't respond, and they had to enter this trial with moderate or worse disease. So they could not have improved. Some of those patients went on to improve and to meet the stringent criteria of an OLA of "none" or "minimal;" in fact, apprxoiamtely 15 percent of those patients did rech that criteria, and then those patients had a sustaining of the effect in the post-treatment phase.

So, it does suggest that 12 weeks may not reach--all the patients may not have their maximal response in 12 weeks.

[Slide.]

This is looking at the open-lablel study. And, again, I think these results are very consistent with what I've already shown you. These are patients who all got 4.5 mg per day. If you look at week 24 here, you have really pretty much the peak efficacy effect. Approximately 20--a little over 20 percent of the patients reach the stringent criteria of "none" or "minimal" disease. And it remains relatively stable throughout the next 24 weeks of therapy. And the effect, again, is somewhat sustained and maintained 12 weeks off of therapy.

[Slide.]

We looked at many secondary measures. Because of time constraints, I can't share all this data with you. But we did show at weeks 12 and 24 that the results were statistically significant in reducation of scaling, erythema and plaque. The

results were statistically significant even in difficult-to-treat lesions, such as scalp, knees and elbows. And the results were sustained t hroughout the post-treatment period in all trials.

[Slide.]

At week 12, nearly 80 percent of the patients were satisfied with their treatment, and there wre statistically significant changes in their quality of life scores. The improvement in the quality of life using a specific psoriasis index called a PQOL correlated with improvement of OLA, and it correlated whether the improvement was only one grade in OLA or higher.

[Slide.]

Just to summarize the efficacy: aprpoxiamtely 20 percent of the patients achieved "none" or "minimal" disease. Approximately 50 percent--or a little over 50 percent--had at least moderate--or 50 percent or more clearing of their disease. There was a significant improvement in plaque elevation, erythema, scaling, and pruritus, as well as a reducting in BSA.

[Slide.]

There was a maintenance of effect observed follwoing discontinuation of drug. There was no tachyphylaxis, and really, the majority of patients did not have rebound.

A large percentage of the patients were satisfied with the treatment and had an improvement in their quality of life.

[Slide.]

Now, I'm going to spend some time going over the safety data.

I'd first like to emphasize that we have neaerly 1,700 patients who have been exposed to tazarotene What I'm focusing on in the safety presentation this morning, however, are patients who got at least 4.5 mg, and really focusing on patients who got 4.5 mg for at least 12 weeks; that's 690 patients.

There are also patients who got the drug at least 24 weeks--285; 48 weeks--153; and greater than 52 weeks--101--greater than or equal to 52 weeks, 101.

[Slide.]

We looked at many measures for safety. We looked at adverse efents; physical examinations, vital signs, body weight. We di therapeutic drug monitoring at selected sites. We did x-rays on the spinal and ankle ligaments, looking forcalcifciation or osteophyte formation. That was done on all patients in all studies.

We did DEXZ scans, looking at bone densitometry--again, all patients, all studies. We did ophthalmologic evaluations, and specifically, we did ERGs, only in the long-term study.

We did audiology evaluations, but focused only on the long-term, one-year safety study. And we did neuropsychiatric evaluations on all patients, all studies.

[Slide.]

Oral tazarotene in the clnical trials was very well tolerated. WE had a very low drop-out rate due to adverse events. Less than 5 percent of patients dropped out due to treatment-related adverse events in the pivotal trials, or the 048,

049P trials.

More dropped out in the long-term trials--the six-month trials--6.5 percent. And almost 15 percent of the patients did drop out in the open-label one-year study.

[Slide.]

We had very few serious adverse events in the trial. The adverse events--there were only two which were deemed to be treatment-related. And I'd also like to point out that we did have one death in this trial. The death was secondary to a mechanical failure of a small aircraft, and not thought to be related to the drug.

The two serious adverse events thought by the investigators to be possible due to drug was, one, for a patient who was hospitalized during the post-treatment period for pain secondary to severe ampullary stenosis. The other patient was hospitalized due to hypertension, and it's noteworthy that this patient did have a history of hypertension. Both serious adverse events were resolved.

[Slide.]

There were four pregnancies--or had been four pregnancies with oral tazarotene. Only one of those pregnancies was in the psoriasis trial--this is the 050P, that's the one-year trial. That pregnancy occurred eight weeks after the patient had discontinued drug. And it's notable, because that pregnancy was a result of non-consensual sex, and the patient did choose an elective termination following that.

The other three pregnancies were in the acne Phase 2 trial, which is the 040P trial. One of those resulted in elective termination by the patient; one in a spontaneous termination or miscarriage; and one was a healthy baby born. That baby was exposed in utero to approximately 15 days of drug, and was without any malformations. The child is now 26 months old.

[Slide.]

Adverse events--we measured adverse events in all the trials. I'm going to focus first on the pivotal trial, because it has the placebo control

group. There were adverse events. These were predominantly mild. The most common was cheilitis--or chapped lips. It occurred in 65 percent of the patients. The next most common was headache, and then dry skin; and, less commonly, arthralgia, myalgia and back pain.

Note here, 2 percent of the patients had hyperglycemia, versus placebo, but here were no differences in laboratory values of hyperglycemia relative to placebo. So these are ones that investigators said were adverse events.

[Slide.]

What happens when we discontinue treatment? So, here you have the same data from the previous slide. And what I've shown you here are only those which were statistically significant between placebo and active.

If you see what happens post treatment, you see that they actually all go down. The cheilitis went from 65 to 48. It should be noted: these are all adverse events that occurred at any time during the post-treatment period. Headache

reduced in the post-treatment period to 4.7; dry skin reduced' arthralgias, myalgias--showing that all of these side effects that occurred during the treatment period were reversing with discontinuation of drug.

[Slide.]

What is important, I think, in this case to show you what occurred with adverse events, it's important with what we know about this class of compounds, to say what didn't occur with our drug; what didn't we observe.

We did not observe a difference between tazarotene and placebo in alopecia. Alopecia is a very common problem and a common reason for discontinuing acitretin therapy. We didn't see any endocrine abnormalities. Endocrine abnormalities are common with bexarotene. We didn't see depression, or differences in depression or psychiatric evaluations between the tazarotene and placebo groups, in terms of emotional lability or depression.

We didn't see a difference in elevation of

liver function tests, and we didn't see any changes in visual or auditory.

[Slide.]

So what happened in the long-term studies. Here I'm showing you just the open-label data, so there's no placebo. But you first have those patients who were in the 052P extension study who got placebo the first 12 weeks. So they should be essentially--have the same AE profile as our pivotal trials. Those who got it at least 24 weeks, and patients who got drug at least 52 weeks--or 52 weeks.

Again, cheilitis--very similar. It's the most common side effect with this drug, but it is notably mild. Dry skin--the second; arthralgia, myalgia, headache--very similar to what we showed in the previous slide. So what we also wanted to look for is is there anything new that showed up, and did they change over time?

I think, if you look here, you see that arthralgia does appear to incrase with longer duration of treatment, as does myalgia, and

possibly headache.

[Slide.]

Oh, let me go back one.

[Slide.]

Also, notably, we did see some alopecia out a year; less than 8 percent--still significantly less than observed with the other retinoids, but higher than what I showed you in the placebo trials.

[Slide.]

Liver function tests--this is an importnt one to look at, especially considering this class of drugs. I think these results are very interesting.

First the ALT--transaminases--they were higher--now we're looking at 12 weeks, 24 weeks, and 52 weeks of therapy. They were higher in the placebo group than any of the treatment groups.

AST--the other transaminase--was relatively stable between the placebo-control trial at 12 weeks, but does look possibly like it goes up at 52 weeks--excuse me, at 24 weeks or 52 weeks.

But I think when you look at that you have to remember there's no placebo group, and over a year, at any one time, an individual laboratory value may spike.

Similar, GGT; LDH we didn't see much; bilirubin--direct, indirect, total. The only one that we do see a really change was alkaline phosphatase, which was elevated relative to the placebo in the treatment groups at 12 weeks in the 52-week study--up as high as 14 percent.

[Slide.]

We looked at all laboratory values. I showed you the ones that were statistically significant. Looking now at all laboratory values, in the tazarotene versus placebo trial, what else do we see?

Well, creatinine phophokinase--higher in the placebo group relative to the tazarotene group This is also unique. I think if you think about isotretinoin and elevations in creatinine phosphokinase are a known problem.

Triglycerides--22.8 percent versus 16

percent. What does that mean? I'm going to go into that a little more detailed in the next slide. ALT--worse in the placebo versus tazarotene; bilirubin worse in the placebo group versus tazarotene.

So let's look at that triglyceride elevation, which was statistically significant.

[Slide.]

We looked at the triglycerides in many different ways. But I think that looking at it up here, the way I presented it, is instructive. We looked at patients who were elevated above 250mg/dL, and those who were elevated at greater than 500mg/dL, assuming that around 500 would at least be a definite trigger for a patient to either leave the trial or to go on a second drug.

What you can see is that 30 percent of the patients in the tazarotene-treated group were at least--were above 250, versus 23 in the placebo group. And that was statistically significant.

But if you look at the higher elevations, you see that they were actually equal between the

two treatment groups, suggesting that there is some elevation of triglycerides, but those elevations are modest.

[Slide.]

We looked at the effects on bone. As I mentioned earlier, we did DEXA scanning, to look at bone mineral density in the lumbar spine, total him, and htefemoral neck. And we did x-rays of the spinal and ankle ligaments for calcification, and looked for osteophyte formation.

[Slide.]

Focusing first on bone mineral density, the data demonstrated that after 12 weeks of treatment there were no differences in the median percent change in bone mineral density in the spine or the femur. In the hip, there appeared to be in increase in bone mineral density, but that increase was very small, and not--it was statistically significant, but very unlikely not clinically meaningful.

In longer-term studies, at 24 weeks and 52 weeks of therapy, we did show that there was a

change in the median percent of the bone mineral density. But those changes were very small, and they occurred only in the femoral neck and total hip, and not in the spine.

We did see gains or losses--and there are many ways to look at this data, and we can explore this later this morning--many ways to look at the data. But if you look at patients who had gains or losses greater than 5 percent, we saw that in all three areas. We did see that there were more individual losses rather than gains in the total hip and the femoral neck, and that there were no differences for the spine. So the hip and the femoral neck seem to be the key areas where there were any changes at all.

[Slide.]

In this slide I'm showing you the mean percent change in the bone mineral density, and that these mean percent changes were very small. The scoring system is a g/cm
2 And you can see where the baseline screening visits were on average there, and then what athey changed.

First of all, note the lumbar spine. There were no statistically significant changes, and they were very small. If you look at the total hip, there were statistically significant changes at week 24 and 52, but they were changes of .45 percent.

If you look at the femoral neck, there was a change at 233k 24 of close to 1 percent--.92--and at week 64, 1.27. But at week 52, nothing. So these are decreases--small percentage decreases in the bone mineral density.

[Slide.]

So, to summarize those findings, there were median percent changse, but they were very small. They occurred only in the femoral neck and the total hip, but not the lumbar spine. We think that these changes really are--could easily be explained by differences and variance that you would expect in the normal population.

There are individual gains and losses of greater than 5 percent, but they are probably also within the normal variation.

We also have data--our data demonstrates that these changes are not associated with the incidence of fractures. They're not associated with the incidence of osteoporosis. They don't--there doesn't seem to be an age association, a gender association, or an association with medications such as a history of systemic corticosteroids.

[Slide.]

Now, let's look at the data for hyperostosis. These were the x-rays. What we've shown here--we looked a couple things. We looked at what was the existing hyperostosis; so, really, the prevalence, and how did that change through time, as well as looking for changes in increases in individuals.

Looking here first at the 050P study--this is the one-year study--and we show that at baseline--you know, between 50 to 58 percent of there sites looked at--so, the cervical vertebrae, the plantar ankle or the dorsal ankle had pre-existing either ligament calcification or

osteophyte formations. That number seems high, but it's probaly indicative of both psoriasis patients, as well as age. AN dit is within the reported numbers for that population.

But look at what happens at weeks 24 and 52, the numbers really don't change. The cervical vertebrae go up slightly to 63. The plantar ankle goes up and down at 54. The dorsal ankle stays relatively the same.

So we didn't show that when you look across at what you consider the prevalence for this population, over one year they did not change.

[Slide.]

So did they actually worson? So they didn't get more, but did the disease worsen? Here, I've made a cut-off to show you the dta at greater than a one-grade change, which would be more significant than less than or equal to one.

You can see that at weeks 12 and 24, we didn't see anything. At week 52, there were some modest increases: the cervical spine, there was a 5.2 percent of the patients had an increase in

calcification or osteophyte formation. In the plantar ankle there was a 1 percent. So there were a fwe significant changes---- statistically significant.

[Slide.]

I'm showing you--reviewed a lot of the adverse events here. And I think what we feel that this shows that there were some adverse events that you would expect to see with a retinoid, but there were other adverse events that you would expect to see that we did not see, which points to, really, our specificity ata the RAR á, .

What we dind't see was hepatotoxicity, hypercholesterolemia, or changes in thyroid function, which are RXR or RARà-mediated adverse events.

What we did see are RAR á and adverse events. We saw cheilits. We saw some arthralia, some myalgia, some statistically significant changes in hyperostosis and bone mineral density, which may or may not be just due to normal variation in this population.

[Slide.]

So what are we recommending for monitoring, based on what I've shown you today?

Allergan is recommending that patients on oral tazarotene do not need routine laboratory evaluations, unless they are an at-risk population. If thte patient has a pre-existing condition which would result in elevated hypertriglyceridemia, they would need to be monitored, such as patients with diabetes or they start the drug with hyperlipidemia.

We don't recommend routine bone mineral density or x-rays for our patients. Again, unless they have a pre-existing condition which put them at risk, such as arthritis or osteoporosis, or a propensity for osteoporosis.

We do recommend period monitoring for patients who have a significant change in symptoms, or are on this therapy long-term.

[Slide.]

And now I'd like to just turn my talk towards the Risk Minimization Action Plan for oral

tazarotene.

[Slide.]

Oral tazarotene is a probable human teratogen, and I'd use that qualifier because technically speaking, until you see a teratogen, or you see a malformed fetus, it is "probable." We feel it's probable due to the class of drugs and what we know.

Because we're looking at psoriasis__AND I think this is something that was mentioned in the introduction--you need to frame this ddrug and this risk in the frame of what physicians already use for treatment of psoriasis, and we commonly use two other drugs which are teratogenic; specially, methotrexate and acetretin.

Allergan feels that oral tazarotene is a very viable and important treatment option for women of childbearing potential. We feel that because it has a short half life and would be washed out of the body quickly, that it would be a useful medication for this population. And because of that, we are in support of having a Risk

Minimization Action Plan to protect the vulnerable patients.

[Slide.]

The goals of our program are that no woman who is pregnant shall be prescribed or dispensed tazarotene. Women who are taking oral tazarotene shall not become pregnant.

[Slide.]

Now, there's, I think, a little bit of possibly confusion in what I'm going to show you now, and what was proposed originally in our NDA. And I've got some slight changes to what was in your briefing package. I apologize for having changes, but as many of you know, sitting around this table, this has been an evolving process. And I think this is a great opportunity for me to thank Khalyani Bhatt, because she has arranged many, many discussions between the Derm and Dental division, the Drug Safety Group and Allergan as we've evolved with this process. And she's been really terrific at doing that.

We based our NDA, originally--which was

filed in November of 2003--we based that NDA on the current isotretinoin program at the time, which was the SMART program. We updated--and we've been evolving--since the February 2004 meeting. We wrote our briefing package with modifications of the program that was in our NDA to account for the changes in February. Since even submitting the briefing package, we've had teleconferences and actual meetings with the Division, and we've actually modified it a little bit more. They are slowly getting us to where they want us to be--is what I like to say. We've had lots of discussions with Dr. Wilkin.

So I'm going to highlight where the differences are in the program.

[Slide.]

First of all, we're now recommending a mandatory registry for all patients. And this is something that we're interested in certainly discussing with the committee. Our original proposal was just for women of childbearing potential; a targeted education program for all

patients; a mandatory registration and certification for physicians and pharmacies; a verification of all patients qualification at the pharmacist through an interactive technology-based system. This is the other difference--they're in italics. Prior to this, the proposal, I believe, in your briefing package was only for women of childbearing potential. A laboratory-based pregnancy test, which is hard linked between the pregnancy testing and the drug dispensing.

[Slide.]

Managed access--this is really our main difference between the recommendations that were presented by the isotretinoin--for isotretinoin at the February meeting--and that is a drug supply. We're recommending for women of childbearing potential that they get a one-month supply with no refills. However, for patients who are males, or women not of childbearing potential, we're recommending that those patients be allowed up to two refills. And this really is--the difference between, say, an acne population and psoriasis.

We're also proposing a pregnancy exposure registry, which is designed according to the FDA guidance. It's a proactive study that will follow up each pregnancy throughout its duration. We will also look at program effectiveness metrics. We'll look at pregnancy rate; knowledge, attitude and behavioral assessments; process compliance measures; and we'll do root cause analysis.

[Slide.]

As I've mentioned, our program really has all the essential features of the isotretinoin program, based on the recommendations of the committee in February of 2004. But there are, I think, important things that we need to consider, and that is that that program is designed for an acne population. Isotretinoin is prescribed for 20 weeks--you know, give or take some time, depending on a clinician or a particular patient. And monthly office visits for six months, while burdensome, are not overly burdensome.

With psoriasis, which is a chronic lifelong disease, requiring a patient to come in

every month is burdensome. It's burdensome to the patient, to the physician, to the health care--you know, health economics.

The majority of our patients are over 40 years of age--or that's the average age is above 40 for patients on systemic medications. So I think we really need to consider this, because you could have the unintended consequence of a physician not prescribing tazarotene, or a patient not willing to come in once a month for oral tazarotene and, in turn, getting a drug which could possibly be less safe for them, or not having any systemic therapy when they need it.

[Slide.]

So we have a slightly customized program, and we'd like to have discussion with this. And we want to work with the agency to have a program that protects a vulnerable population. We've very behind that. But we'd also like a program that is practical; one that could be implemented by patients, by health care providers and pharmacists.

And we'd also like to propose, and discuss

today, whether a program for all oral systemic retinoids--or even all teratogens used in diseases--should have the same program to avoid confusion in the marketplace.

Thank you.

I'm now going to turn the podium over to Dr. Alan Menter to discuss the risk-benefit assessment of oral tazarotene.

Oral Tazarotene Risk Benefit Assessment

DR. MENTER: Thank you, Dr. Walker.

[Slide.]

It's obvious, when confronted with clinical research studies safety data that we as clinicians, and you as a panel, have to make an assessment as to whether the drug in question--i.e., oral tazarotene--is worthy of usage in our psoriasis armamentarium for patients with moderate to severe psoriasis.

What I'd like to now do in the next six to seven minutes is review the data and discuss this issue relating to risk-benefit assessment. And I really would like to wear my psoriasis advocacy

hat. I am--part of the work I do with the National Psoriasis Foundation, who is represented here today, is direct the advocacy group for the medical advisory board. And my two colleagues, who are here as consultants today, Dr. Krueger is immediate past president of the medical advisory board for the National Psoriasis Foundation, and Dr. Lebwohl is currently the medical director. And we are very, very involved in advocacy issues relating to psoriasis patients and safe treatment for our psoriasis patients.

So I think we've heard--both from Dr. Cook and myself, and from Dr. Walker--that we are dealing with a disease that has physical and psycho-social implications; that is lifelong; and we currently have good therapies for psoriasis but we do have some limitations, and we certainly have an underserved population of patients who have moderate to severe psoriasis, as has been discussed.

[Slide.]

Dermatologists have used retinoids for

many, many years--for decades. And, as I'll discuss shortly, we are relatively comfortable with the use of systemic retinoids for the diseases that they are currently available for. However, I do believe we now have a unique retinoid. And as has been discussed by Dr. Walker, because of its unique receptor selectivity, we believe that some of the side effect profile that we've come to expect with retinoids have been minimized, as has been discussed in the clinical data shown by Dr. Walker.

We know that this drug has significant improvement, both short-term and long-term, on the clinical signs and symptoms of psoriasis. And the vast majority of patients respond. Certainly--as has been discussed--very few drugs clear patients, short-term, long-term, on a long-term basis. And we have a drug here that has a significant in the vast majority of patients with psoriasis--dealing with patients with monotherapy, with systemic retinoids.

It is also important that dealing with a lifelong disease that we do have a drug that does

not lose efficacy over time. And we now have one-year data that shows that; that we do not lose efficacy. And also, when the drugs are stopped for whatever reason, that there's no risk of the disease rebounding or producing the erythrodermic form of psoriasis that Dr. Cook showed, which we sometimes see with some of our other systemic medications.

[Slide.]

you've seen multiple clinical slides of the clinical effect of psoriasis, both from a physical point of view as well as from an emotional point of view.

[Slide.]

So, as I've mentioned, we've had retinoids available for the past 20 years. And the current retinoids that are available--etretinate is no longer available. It's superseded by acitretin--altrans retinoic acid--ARTRA--is a drug that has recently been made available for the treatment of promylocytic leukemia. And, of interest for us dermatologists, that this is used

in conjunction with an old drug that dermatologists have used for a long time--arsenic--to maintain patients in control with a rare form of leukemia.

Bexarotene is available for cutaneous T cell lymphoma. And isotretinoin, as we all know, for acne.

However, the only drug in this group that is approved for psoriasis is acitretin. And because of the concerns of some of the safety issues to retinoids and other drugs, we do believe that the improved safety profile of oral tazarotene does warrant consideration as a new systemic form of therapy for psoriasis.

[Slide.]

So, what I'd like to do now is just contrast the oral tazarotene--bring up a few key points related to oral tazarotene, and how it does compare with some of the other retinoids that I've mentioned here now, particularly acitretin, a drug that we all enjoy using and have used, as I said, for many, many years, and very comfortable using acitretin, as we will do in the future, as well.

However, the distinguishing features relating to oral tazarotene I think are shown here on the table. I think one of the most significant features which opens up this drug to females of childbearing potential is the short half-life of the drug. The drug, as you can see, has a short life of seven to 12 hours, and the majority of the drug is eliminated within five days, contrasting with the longer half-life of the other retinoids, particularly, as is shown here, acitretin.

Ethanol--this may not be considered a big issue, but when confronting patients in the clinic on a day-to-day basis, and making choices for therapy with out psoriasis patients, the question of "can I drink socially?" "Can I have a drink?"--they cannot with methotrexate. This is not allowed with methotrexate. The label specifically precludes social alcohol of any kind with methotrexate therapy. And because of the conversion of acitretin to atrentinate, and the fat storage of this drug, alcohol is also precluded in females of childbearing potential who utilize this

drug. And this may take two to three years for elimination--hence, the three-year exclusion when using acitretin, which will not be an issue at all with oral tazarotene.

I mentioned earlier that as patients age lipids becomce an issue with patients, and we're frequently confronted with patients on lipid-lowering agents as the population ages. And I think the fact that we do not have this concern, to a major degree, with acitretin [sic], again, is I think, a significant improvement over other retinoids that we currently have available to us.

[Slide.]

Liver toxicity--patients develop hepatitis C, and we are frequently faced with issues relating to patients with abnormal liver function tests. Patients certainly have been shown, in the clinical studies that Dr. Walker has discussed, to show minimal changes--short-term or long-term--in liver function tests between placebo and oral tazarotene--as compared to one-third of patients with acitretin.

The alopecia issue, I think, is a big concern for us. Probably, if one had to ask me, "What is the single most common cause for discontinuing retinoids?"--other retinoids, particular acitretin, in psoriasis patients--it's alopecia, particular females, who certainly do not enjoy losing their hair. And this has become a big issue, and we have to tailor--drop the dose of acitretin to minimize this concern, a mucocutaneous side-effect concern. And the very fact that we have minimal alopecia with oral tazarotene, I belive, again, is a significant distinguishing feature.

And, finally, the other mucocutaneous side effects--outside of the cheilitis, the dry skin, the pruritus and--certainly for the ophthalmologists in the audience--in the panel--the dry-eye syndromes and the problems we have with dry eyes, in consultation with our colleagues in ophthalmology, is of some concern with most of the retinoids, but does not appear to be a significant issue with tazarotene.

[Slide.]

And I think the most critical issue that's obviously facing the panel today, and that has been discussed in the risk minimization and risk management plan as outlined by Dr. Walker and her colleagues from Allergan, is the comprehensive nature of the plan that has to be brought into being, in order for us to be able to utilize retinoid therapy in the future.

So, basically, females currently are excluded from both methotrexate therapy, and all females of childbearing potential--and, as I mentioned earlier--are also excluded from acitretin therapy. And I do believe this is a significant proportion of the patient population: young females of childbearing potential, who no longer have to be excluded from retinoid therapy because of the selective nature of this drug.

[Slide.]

In my final few slides, I do strongly believe, again, as a patient advociate--which is what i believ we all should be thinking of--is that

this drug has shown sustained clinical benefit of a course of one year. And it's likely to be continued, as clinical studies continue; that ongoing therapy with this drug does show further response. There has been a very high patient acceptance for this drug, both because of its clinical responsiveness, and because of its lack, particularly, of mucocutaneous side effects and alopecia. And I think the low ddrop-out rate--less than 15 percent over a one-year period--I believe is a very strong guide to the patient acceptance of this drug, and is a very low rate as compared to many other systemic agents.

[Slide.]

Discussing, again, the female issue relating to it, we do believe--and I do believe, I believe Allergan believes, my colleague believes--that this is a drug that should be made available for that population group who have hitherto excluded from therapy; i.e., females of childbearing potential. And with the risk minimization action plan proposed, I do believe we

as clinicians, and the dermatologists in the audience, will feel comfortable prescribing a retinoid drug, bearing in mind that we have a great deal of experience with the use of retinoids previously, in psoriasis and other conditions.

And, finally, the point relating to alcohol consumption, I believe I've touched on previously.

[Slide.]

So, in summary, oral tazarotene does have an improved clinical and adverse event profile over other systemic retinoids.

The issues that concern us--namely, lipid metabolism, hepatotoxicity, mucocutaneous toxicity, alopecia--appear to be extremely low, and a significant improvement over what we currently have.

And some of the other issues that we need to consider, obviously, are the bone mineral density. And I think Dr. Walker has outlined these issues to us.

[Slide.]

So, my final concluding slide, is that based on what we've heard today, based on the efficacy data and the safety data, and the risk minimization action plan that has been proposed, tazarotene capsules, I do believe--and I believe my colleagues who are with me today believe--should be made available, not just to a small select group of patients, but to all patients who have moderate to severe psoriasis; that a group of patients who I believe currently is vastly underserved.

Thank you for your attention.

Discussion of Allergan Presentation

DR. STERN: I'd like to thank the sponsor, and open to the panel for questions that are directly relating to information presented by the sponsor. We'll have lots of time in the afternoon to discuss the global issues. But points of clarification, additional data that might be helpful.

So--Dr. Honein?

DR. HONEIN: Yes, I'd like to know the denominator for the three pregnancies that occurred

in the Phase 2 acne trials, and the one pregnancy that occurred in the psoriasis trials; and, specifically, the denominator of reproductive-age women.

DR. WALKER: Well, I'll be answering questions from back here, if you'll give me one minute.

The psoriasis trial, there were 263 patients who were enrolled in that trial, but how many of those were women--80 percent of them were males. So, roughly 20 percent. And I can get you that exact number in a moment.

In the acne trial--that doesn't break down the gender. We need the gender.

In the acne trial, that was the 049P, that was a dose-ranging Phase 3 trial, and that was also fewer women than men. Yes--I'm sorry--I don't have the exact numbers for that trial, but there were, I think, 183 subjects in the trial total, and fewer than half were females, roughly 40 percent. But I don't have that exact number.

I will point out that there was a

risk-management program piloted in the psoriasis trials, but not in the acne trial.

DR. STERN: Dr. Ringel?

DR. RINGEL: I actually have three questions.

The first has to do with the makeup of the target groups for P 048 and 049. On page 31 of the Allergan handout, we are told that certain--that patients were on certain concomitant medications, and certain concomitant medications were excluded. Likewise, certain conditions were excluded.

The first question is: I'd like to know what were those conditions? What medications were excluded? And what medications were specifically allowed?

DR. WALKER: Patients could not be on systemic medications which would affect their psoriasis. And there were--could you bring up what the--the full list of exclusion criteria in a moment--but patients couldn't be on systemic medications which would affect their psoriasis, and

they could not be--which would be, really, primarily, corticosteroids or methotrexate, acitretin. So any drug that would affect their psoriasis, there was a washout period for systemic retinoids which was longer--there was a washout period for cyclosporine and for methotrexate in the trials.

And you asked me another question?

DR. RINGEL: Umm--

DR. WALKER: Oh, and conditions.

DR. RINGEL: Conditions.

DR. WALKER: Their psoriasis could not be rapidly increasing or decreasing--which does somewhat eliminate, say, a guttate psoriasis, because that often is rapidly changing. They couldn't have a condition which would interfere with their ability to do x-rays. So if they had, say, a plate in their hip or their ankle which would inhibit the ability to read the x-rays for calcification, they were excluded.

If they had unstable psychiatric disease, they would be excluded--or any condition that the

physician felt would make them unreliable or unable to participate in the trial, they were excluded. But that's it.

It was somewhat open-ended that the physician could exclude people.

DR. RINGEL: How about alcohol-increased liver function tests at baseline, or triglycerides at baseline--alcohol abuse?

DR. WALKER: They could use alcohol in the trial. That wasn't exclusion--

DR. RINGEL: How about if they overused alcohol?

DR. WALKER: We didn't ask, one way or another, about overuse. That--you know, what is "overuse" can also be a little bit of a nebulous thing. But, no, they were not excluded for alcohol use, and we didn't take a definite history of alcohol use.

Slide up, please.

The exclusions will be on the screen there. I went over most of them.

Umm--I'm sorry, I'm going to have you--I

got off track on the alcohol use. You asked me another question. Specifically, alcohol use and--oh, triglycerides.

There was an exclusion for triglycerides greater than 500 mg at baseline. They could have elevated liver function tests or triglycerides if the physician felt that they were stable. So, they were either within normal limits, or the physician felt that patient was stable to go on drug.

Patients were allowed to have hepatitis C in the trial. They were allowed to have elevated triglycerides below 500 and other labs.

For anyone here who's done extensive psoriasis trials, if you don't allow some wiggle room around labs, you'll never be able to recruit patients, because they do have many co-morbid conditions. They have, often, diabetes and other things.

So, yes, we did allow that if they were stable.

DR. RINGEL: And how about topicals? Were all topicals allowed?

DR. WALKER: No. No topicals were allowed except emollients. So there was no topical tazarotene, dovinex or corticosteroids allowed.

On an occasional basis--and we do have that data--some patients used emergency topical steroids for, say, poison ivy or something like that, for very short periods of time. And those protocol deviations were all noted.

DR. RINGEL: The other major question I had was that I don't understand how you applied OLA to systemic medication. It makes a lot of sense to me for a topical medication, because you can take a target lesion and follow that lesion. But, as any dermatologist on the panel will confirm, psoriasis in the different body parts doesn't necessarily resolve at the same rate. So you could have wonderful clearing on the body, whereas no clearing at all on the sacral area.

So I was wondering how--in other words, when you described how the OLA was applied, which only takes into account an individual plaque, it seems to me, did you follow the worst plaque? Did

you take an average? Did you--how did you do it?

DR. WALKER: It's a clinical assessment, and it's a clinical integration. And so, essentially, the physician looks at the patient and does--you know, not a numeric average, but an average--you know, overall average based upon, really, the worst lesion.

That can work, of course, for and against you. If you take the worst lesion, it's certainly harder to have a clinical success. But it is driven by plaque, and it is an integration of the entire body.

We did learn in the topicals that actually there were patients in the topical trials who had 80 percent body surface area, where they applied their tazarotene. Those were the higher patients. But the scoring system worked there. We piloted it in the Phase 2 trial and showed that it did work.

When we separated out plaque, erythema, scaling, we separated out the target plaques, the results were essentially the same for all groups, which demonstrated to us that it did work that way.

It is a new measure, but it does have some clinical relevance, and it did work in the trials.

DR. RINGEL: So if there's someone who had complete clearing on the trunk, and no clearing at all on the knees--which isn't unreasonable--someone would kind of just have a gestalt of what it was and--

DR. WALKER: No, they would not have achieved clinical success as we set of "none" or "minimal" disease. If they had complete clearing everywhere, but then had severe plaque on the elbows, they still would have an OLA of "severe." They had to bring all of the plaques down.

DR. STERN: Could you just tell us what the "intra" and "inter" rate of reliability was of the score so we can get some idea, you know, really what you mean by "gestalt," and how well tested this is as a metric.

DR. WALKER: We did not do a specific test to validate the scoring system separately, where we looked specifically at inter-intra related reliability. We do divide the scoring system out

in the trials by investigative site, and saw no difference from site to site. But we formally did not do that.

DR. STERN: And the rationale for not looking at the test characteristics of this, in terms of reliability, both inter and intra rate of reliability for a non-conventional measure, where--

DR. WALKER: When we adopted that measure for the oral systemic development of tazarotene, the measure was no longer non-conventional to us, because we had used it in the topical.

The scoring system has been used for other systemic drugs. It was used in the Raptiva Phase 3 pivotal trials. It wasn't called an "overall lesional assessment," but--yes.

VOICE: What did they call it?

DR. WALKER: An OLS--an "overall lesional--"--I don't remember what the "s"--"severity" score. So it was used--and actually the results were very similar in their trial to using the PASI score, in the sense that it was effective for their drug also. And I think,

Dr. Lebwohl--do you have another question--

DR. LEBWOHL: To address Dr. Ringel's comment: when we have looked, in previous studies, at elbows and knees, which you'd expect to respond more slowly compared to trunk, we didn't find a a big difference. However, there are certainly areas that clear more quickly, such as the face or intratrcianous areas, that routinely clear more quickly than other body sites. And I think the word "integrated" was key here.

The assessment tool that was used here was in response to, basically, dissatisfaction that was expressed even at the FDA. In fact, I think, Dr. Stern, the quote from you is: "PASI is passe," was a quote I believe you said.

A difficulty with assessment tools--and this one did seem to work. And I have seen a slide of inter-investigator variation, or within one investigator, variation. But to address directly your comment, I can't recall a single patient who had severe knees and mild trunk after treatment, unless they started out that way.

DR. STERN: Dr. Wilkerson is next.

DR. WALKER: I'm sorry--can I answer Dr. Honien--I hope I said your name right--her question. I have the numbers. I'm sorry to interrupt you.

In the 050P study, there were 83 females out of 263 total patients. And in the 040P acne trial, there were 81 femals out of 181 total patients.

I'm ssorry for interrupting you.

DR. HONEIN: Those were reproductive age, or all women?

DR. WALKER: All women. In the acne trial, they were prdominantly of reproductive age. The breakdown for reproductive age in 050P will be a smaller subset.

DR. STERN: I'm sorry--Dr. Wilkerson, please?

DR. WILKERSON: In regards to the alkaline phosphatase, what was the fractionation of the abnormal values?

DR. WALKER: We did not fractionate the

alkaline phosphatase for patients in this trial. We did do fractionation in our 040P--our acne trial--for bone and liver, and saw no differences. But we did not specifically fractionate the alkaline phosphatase in the 050P open-label trial.

DR. WILKERSON: So we're making an assumtion that since liver function tests were not abnormal, that the abnormal alkaline phosphatase fraction is bounded?

DR. WALKER: That is the conservative assumption that we have made.

DR. WILKERSON: I mean, I'm assuming that you have serum placed aside that's been frozen, or--

DR. WALKER: We have serum not sepcifically saved aside for these patients. And I don't know right now whether we could go back and sub-fractionate those alkaline phosphatases for all patients.

DR. WILKERSON: I mean, this is obviously--outside of the pregnancy--you know, one of the big concerns about this drug long-term. I mean, you

know, you're talking about a fairly inexpensive laboratory test. I mean, the fact that your GDTs also rose is sort of suggestive of a hepatic--I saw those GDTs were up at one point also, which is somewhat of a crossover.

So I think you have an ambiguous laboratory situation that needs to be clarififed for the long term.

DR. WALKER: Slide up, please?

DR. STERN: Dr. Levin?

DR. LEVIN: My questions relate to the RiskMAP proposal, and I might--if you'd rather follow this line and I'll come back later on.

DR. STERN: I think in the afternoon we'll probably be spending a fair amount of time on that, and we'd like to talk more about data presented in the presentation.

Dr. Furberg?

DR. FURBERG: I had a similar question. I was interested in the experience of the--you piloted the risk management program, and would be interested in knowing the experience; how was the

adherence with mandatory registration of patients, registration of physicians, pregnancy testing and so on.

But--if you want to answer now, later--

DR. STERN: I think probably more in the afternoon for that.

Dr. Katz?

DR. KATZ: I have two questions: one, in the mechanics of evaluating patients, did the same investigator evaluate the improvement as evaluated the side effects? Or was there--

DR. WALKER: It was the same investigator who did that. They were not required to be separate.

DR. KATZ: So this would not be put out as a double-blind evaluation. It was--

DR. WALKER: Well, it was double--

DR. KATZ: --placebo controlled.

DR. WALKER: --yues, placebo controlled, blinded in the sense that the investigator didn't know what the patient was on--tazarotene or placebo.

What your saying is would they know because a patient had chapped lips, say, that they were on active. And I don't know if you'd want that now or in the afternoon, but we--

DR. KATZ: No, I just wanted to make sure that that was made clear, that the investigator evaluating the side effects also was evaluating the improvement, negating any double-blind assertion.

DR. WALKER: The same investigator--

DR. KATZ: The other question is: did the company have any expert in bone metabolism consult regarding the concern that will come out in the further discussion.

DR. WALKER: We've had several experts look at the bone data with us, from statisticians who've looked at the data normalized across populations. We've got some experts with us here--

DR. KATZ: So will we be informed of their considerations? At this meeting today?

DR. WALKER: Umm--well, we have a lot of the data--I'm not exactly sure--do you mean, will you be hearing--

DR. KATZ: My question is--

DR. WALKER: --from an expert that will--

DR. KATZ: Yes, will we be informed of what their evaluation of--

DR. WALKER: Yes.

DR. KATZ: Thank you.

DR. STERN: I'd like to close this section with a few questions of my own, in spite of Ms. Topper says to me.

[Laughter.]

The first is: you talked about 79 percent or 80 percent of people indicating--patients indicating satisfaction. I don't think you presented the--as I recall from the briefing document--in fact 53 percent of the placebo people had similar ones. So it was a 27 percent difference, not some larger difference.

The second is: you talked about a correlation between quality of life and the OLA score, but I didn't hear how much the quality of life instrument shifts were, and what, in fact, that correlation was; whether it's an r-square, or

whatever measure you used. So I'd be very intrersted in that.

And I guess the third is one that has to do--aside from half-life comparisons between tazarotene and acitretin which were featured in the final presenter is--we have to remember that, except for the half-life considerations, that retinoid side effects are very much dose-related. And we've only heard about one dose of tazarotene, tazarotene in terms of efficacy and safety. And the information on acitretin, I believe, comes from the literature that deals with doses that are literally more than an order of magnitude different--some doses being as low as 10 mg in use, and other doses being well in excess--up to 150 mg in use.

So I think making comparisons other than things related to half-life and the accumulation of drug in pregnancy for all the other endpoints, it's very hazardous to do without head-to-head comparisons--and particularly, in the absence of knowledge of where is this dose in efficacy or in

any other way relative to the safety data from the competitive drugs.

So if you could--that's a comment, but if you could answer my other questions.

DR. WALKER: I certainly--slide please--satisfaction rates--you're correct, there was a high placebo satisfaction rate. If we look at patients who were extremely satisfied, very satisfied or somewhat satisfied, the placebo is the light blue bar, and the tazarotene-treated group is the dark blue bar. And the difference is--although, you know, and you clearly described what the data was if you take all patients who were satisfied. This is actually just breaking us down.

You can see they are statistically significantly different from placebo for "very satisfied," "somewhat satisfied," and "extremely satisfied." However the differences aren't 80 or 90 percent--as you mentioned.

If you would put up the PQOl--put that slide up, please?

[Slide.]

This is looking at the PQOL, and correlating it to improvement--which I did mention, as you rightly mentioned. If you look at the placebo--this is looking at the score--and the placebo group compared to patients whose PQOLs--this is looking at change--all right?--or reduction in PQOL score which is an improvement in the quality of life--placebo had less than a minus-1 improvement--.84. Patients who had a one-grade improvement were 1.87; a two-grade improvement, 2.43; a grade of "none" or "minimal," 2.96.

So you can see that the patients had an improvement of their PQOL score with any improvement, and it was certainly greater as they went to "none" or "minimal" disease.

DR. STERN: That wasn't quite my question. My question is: what's the correlation between a PQOL and an OLA score, rather than does PQOL go in the same direction. And I think those are--you know, essentially, a patient who gets an improvement in their OLA score, are they going to

also say life is better in terms of impact of psoriasis at an inter-individual.

So I'm really looking for some non-parametric equivalent of an r-square.

DR. WALKER: We did not do that.

DR. STERN: I'd like to then--we're only five minutes behind--[laughs]--which is pretty good-

[Laughter.]

--and have us have a 15-minute break, and we'll start very promptly at 10:20.

[Off the record.]

DR. STERN: We'll now be hearing from the FDA, with Dr. Yao presenting the FDA's presentation concerning toxicology studies of tazarotene.

FDA Presentation

Toxicology Studies of Tazarotene

DR. YAO: Good morning. I'm Jiaqin Yao from FDA.

Today, I would like to talk about toxicology study of tazarotene.

Tazarotene was previously developed for

topical use. This NDA submission is for oral administration. So the sponsor has tested the tazarotene by oral administration in rats, dogs and monkeys for up to one year.

[Slide.]

The study showed that oral tazarotene has a typical toxicity of other retinoids. The maximum system exposure (AUC) to tazarotenic acid, which is the major metabolite of tazarotene is almost as similar of weight of small or the human systemic exposure, which is in single dose 4.5 mg.

The primary target organ or system included bone, liver, kidney, heart, thymus and skin.

Tazarotene was tested to show that no genotoxic effect, and in carcinogenic studies in rates and mice showed that there's no significant increase in tumor frequencies.

In the next couple slides I will focus on the reproductive toxicity induced by tazarotene.

[Slide.]

Study has been done in male and female

rates at the dose 1mg/kg by oral. So AUC--that means system exposure is three times over human exposure AUC which is 4.5 mg/day. So that means the step exposure is only about 30 percent of human.

They show that the mating performance and fertility is no change at this dose.

[Slide.]

As the dose incrases to 3 mg/kg per day, the AUC is 0.7 times our human AUC by oral tazarotene at 4.5 mg, it shows that there is a sperm count and density decrease.

Studying the female rates at a dose of 2mg/kg per day by oral, AUC is 0.6 times human AUC, the mating performance and fertility does not change. But we see some development toxicity.

[Slide.]

Studiies have also been done in toxicity in embryonic development--developmental toxicity. The study has been show in female rats at 0.25mg/kg by oral. The AUC is 0.2 times human AUC. We saw some development delays, teratogenic effects, and

post-implantation loss.

[Slide.]

Another study in female rabbit, at 0.2 mg/kg per day by oral, the AUC is 4.7 times human AUC, we see similar factor in those studies, just using female rabbits.

Since this drug has been developed for topoical studies, the sponsor has also done some topical studies in the femal rats and female rabbits, at a dose 0.25 mg/kg, theAUC is 0.2. We saw that some fetal body weight decrease and skeletal ossification decreased.

In the studies by topical, in female rabbines, the dose is 0.25 mg/kg, AUC is 2.3 times human, malformations are found in those studies.

[Slide.]

Another study is on the toxicology studies in prenatal and postnatal development. In female rabbis, they have done two studies. The first study is 1mg/kg by oral, but the AUC is 1.1 human AUC. We saw developmental bahavior delays.

Another sutdy used the same dose--1 mg/kg

by oral, the AUC is 0.4 times human AUC, we see developmental delays.

[Slide.]

Another thing I would emphasize a little bit about is this drug on the male reperoductive system. As I mentioned before, at the dose of 1 mg/kg per day in male rats, AUC is 0.3, the mating performance and the fertility does not change. However, at a dose of 3mg/kg per day, the AUC is 0.7, we see some sperm count and density decrease in male rates.

In general toxicology studies, the sponsor has done one study on male dog, which is for nine months. At 1mg/kg per day, by oral, the AUC is 1.9 times human AUC, we see testicular changes. As the dose increases to 3 mg/kg per day by oral, AUC is 4.1 times human, the change is more than 1 mg/kg dose.

[Slide.]

Based on the sponsosr proposal, the maximum recommended human dose for tazarotene by oral is 0.075/kg/day. For other drugs, such as

acitretin, it's 0.83mg/kg, and isotretinoin is 2.0mg/kg. So the daily dose is less than other drugs.

However, when I checked the literature, we find that compared with animal studies in rabbits and rats, the lowest teratogenic dose unit is mg/kg/day, is 0.2mg/kg/day in the rabbits. In rats, it's 0.25 or 1, because the sponsor did two studies. One is 0.25, one is 1.

Compared with acitretin, the lowest teratogenic dose in rabbits is 10mg/kg, and for rats is 150mg/kg. And I also compare with other retinoids, we find that this drug product is--seems is more important as teratogenic in rabbits, and the rats.

Another thing we see those data, we can see that the human is like most sensitive species in teratogenic effect induced by those retinoids.

[Slide.]

So the conclusions from those data, we can see hman may be the most sensitive species for teratogenicity of the retinoids. So when we

consider about the drug dose, tazarotene is more potent teratogen than other retinoids in rats and rabbits, based on the mg/kg/day basis. And tazarotene is a probably human tazarotene.

The next speaker will be clinical pharmacology review by Dr. Ghosh.

Thank you.

Clinical Pharmacology and Biopharmaceutics

DR. GHOSH: Good morning. This is Tapash Ghosh, from the Office of Clinical Pharmacology and Biopharmaceutics, FDA.

My presentation will be to describe the clinical pharmacology and biopharmaceutics aspects of oral tazarotene.

[Slide.]

The focus of my presentation will be pharmacokinetics of tazarotene and tazarotenic acid in plasm; potential for drug-drug interaction; and tazarotenic acid in semen.

[Slide.]

Tazarotene or tazarotenic acid have multiple effects on keratinocyte differentiation

and proliferation, as well as on inflammatory processes, which may conttribute to the pathogenesis of psoriasis. Some of them include: blocking of induction of epidermal ornithine decarboxylase activity; suppression of expression of MRP8, which is a marker of inflammation present in the epidermis of subjects with psoriasis; and inhibition of cornified envelope formation, whose build-up is an element of the psoriatic scale expression.

[Slide.]

This is a schematic of how tazarotene works in our body. Once tazarotene is in the systemic circulation, it undergoes fairly rapid conversion to its active metabolite, which is the tazarotenic acid, with the help of abundance of acerisus enzyme present in our biological system. Then the tazarotenic acid undergoes further oxidation to tazarotenic acid sulfoxide, which, maybe with the presence of the CYPS and FMO enzymes present in the system. And then tazarotenic acid sulfoxide may undergo further oxidation to

tazarotenic acid sulfonates.

Some portion of the tazarotene also undergoes oxidation to tazarotene sulfoxide.

[Slide.]

Tazarotene is orally absorbed, as approximately 90 percent of the oral level tazarotene was recovered in pheresis and in urine as primarily tazarotenic acid and its metabolites.

Tazarotene exposure increases fairly in a dose-proportional manner, following oral tazarotene from 3 mg to 6.3 mg.

[Slide.]

Tazarotenic acid is highly bound to plasma proteins, with an unbound fraction of less than 1 percent.

Following intravenous dose, the apparent volume of distribution of tazarotene and tazarotenic acid was 3.55L/kg, and 0.75L/kg, respectively.

[Slide.]

As I already described, in humans, tazarotene is hydrolyzed quickly and extensively to

tazarotenic acid, which the primary active moiety in the systemic circulation.

In vitro human metabolism studies demonstrated that tazarotenic acid is metabloized to inactive sulfoxide metabolite via CYP and/or FMO enzymes in the liver.

[Slide.]

Fecal elimination is the predominant elimination pathway, with 46.9 percent of the administered oral dose eliminated in the feces as tazarotenic acid. Approximately 19.2 percent of the dose was excreted in the urine as inactive sulfoxide metabolites of tazarotenic acid.

[Slide.]

Following IV administration, tazarotene was measurable in plasma, and was eliminated from the body with a mean terminal half-life of 6.2 hours.

Following IV administration, plalsma tazarotenic acid concentration declined bi-exponentially, with a mean terminal half-life of 13.8 hours.

[Slide.]

Following IV administration, the systemic clearance of tazarotene was 2.23L/hour/kg.

Systemic exposure of the active metabolite, tazarotenic acid, was 21.4 times that of the parent compound.

[Slide.]

This is a profile of how tazarotenic acid gets excreted from the system. An as I have mentioned, this is a normal plot and this is the semi-log plot, just to show the bi-exponential decline of the tazarotenic acid.

The profiles are from day seven and day 13, which shows the profiles on those two days are superimposable.

[Slide.]

As the previous speakers have already mentioned, that tazarotene right now is already approved in topical dosage forms. This table shows the comparison of systemic exposure of tazarotenic acid from different topical formulations.

Without going through each and every

formulation, I want you to concentrate on the last two rows, where .1 percent gel was compared with the 4.5 mg proposed capsule formulation. Here, if we compare the systemic exposure in terms of AUC, it is about one-fourth, and in terms of exposure of Cmax, the topical exposure is about one-eighth, compared to the oral exposure.

[Slide.]

However, the data obtained from topiocal gel was during maximal usage condition, which may not reflect the usual usage condition.

[Slide.]

In terms of drug-drug interaction, there was no interaction found between tazarotenic acid and Ortho-Novum 1/35, and between tazarotenic acid and Ortho-Tri-Cyclen when given as oral tazarotene dose of 6 mg.

However, based on the data, the potential of drug-drug interactions involving CYP450s, especially 2C8 and 2B6, may need to be further explored.

[Slide.]

Now I'll be discussing the tazarotenic acid in semen. Following once-dailing dosing of tazarotene 4.5 capsules for two weeks in healthy male subjects, more than 79 percent of semen samples had tazarotenic acid concentration above lower limit of quantitation, which is .1 ng/ml.

Median semen to plasma tazarotenic acid concentration ratio at each predefined time point from semen samples over the 72-hour period was approximately 1 or less, except at six and nine hours, where the ratio was greater than 1, as dscribed in this following figure--

[Slide.]

--where the ratio, semen to plasma tazarotenic acid concentration was profiled--again, these are the sampling points. And, as we see, for most of the time points, this is the body presence--1--ratio 1. Most of the time points had either 1 or less than 1, but at six and nine hours, the ratio semen to plasma was greater than 1.

[Slide.]

The highest individual semen to plasma

tazarotenic acid concentration ratio 2as 2.8, and occurred between 9 and 12 hours post dose.

The highest plus-or-minus standard deviation, tazarotenic acid concentration observed in semen was 44.4, + 22.2, observed in 16 subjects, occurred at three hours post dose.

The highest individual tazarotenic acid concentration observed in semen was 83.1ng/ml, occured at three hours post dose, in comparison to 1.61ng/ml pleak plasma level from the same study.

[Slide.]

So, therefore, under worst case scenario, assuming an ejaculate volume of 10 ml, the amoung of drug transferred in semen would be 831 ng, which is about 1/5,000th of a single 4.5 mg capsule dose.

The no-effect limit for teratogenicity of tazarotene or tazarotenic acid is unknown in humans.

[Slide.]

Fertilized egg may remain exposed to tazarotenic acid in the semen following repeated sexual encounters.

Finally, the risk to a fetus, if any, while a male patient is taking the drug, or after it is discontinued, cannot be ruled out.

This is the end of my presentation.

Thank you.

So now Dr. Cook is coming for the next presentation

Clinical Safety

DR. COOK: Good morning again.

I've come to you this time to speak on the clinical safety, from the FDA perspective, of oral tazarotene as presented in NDA 21701. Some of the presentation will be a repeat of Dr. Walker's presentation earlier this monrning, but some of it might be a little bit different.

[Slide.]

The safety data base, as you know, is derived from the following four trials: two Phase 3 double-blind placebo controlled trials; and two open-label Phase 3 trials.

[Slide.]

The duration of the trials were 12 weeks

of treatment in the double-blind placebo controlled trial, with a 12-week follow-up; and there were two open-label trials--as described earlier--one 12 weeks treatment with 12-week follow-up, and a 52-week trial with a 12-week follow-up.

[Slide.]

There wre 987 patients treated with tazarotene, and 383 treated with placebo. Tazarotene patients were treated with 4.5 mg once daily numbered 831. There wre 640 patients, or 77 percent, treated for greater than or equal to 12 weeks; 31.4 percent wree treated for greater than or equal to 24 weeks; 18.4 percent for grater than or equal to 48 weeks; and 12.2 percent were treated for 52 weeks.

[Slide.]

Discontinuations accounted for about 54 percent of the patients who discontinued from the trials, either because of lack of efficacy or adverse events. This is in the placebo-controlled trials. And the discontinuations secondary to adverse events in the placebo-controlled trials, it

was 3.4 percent.

In the short-term open-label trial, where patients were taking a second course, versus those patients who were only taking their first course of tazarotene, discontinuations were 6.5 percent for the second-course patients, and 3.2 percent for the first-course patients. So there was a slightly discontinuation rate for those patients who were taking their second course of tazarotene. And, as Dr. Walker mentioned earlier, there was a higher incidence of discontinuation in the long-term, open-label trial.

[Slide.]

Adverse events that led to discontinuations in the long-term trial that occurred for more than one patient included arthralgia, myalgia, arthritis, back pain, alopecia, dermatitis, joint disorder. There were three patients who discontinued for abnormal liver function tests; two for cheilitis, asthenia; two for depression; and two for emotional lability.

[Slide.]

In the pivotal trials, overall, tazarotene group had more adverse events than in the placebo group: 90.2 percent versus 74.6 percent, and this was statistically significant--although I must mention that the trials were not actually powered for safety.

And the significant adverse events that are common to oral retinoids--mentioned earlier--included cheilitis, dry skin, headache, arthralgia. And this shows you the percentage of patients who are on tazarotene--first--experienced the event, versus those on placebo.

[Slide.]

Other significant adverse events in the pivotal trial were myalgia, joint disorder, back pain, nasal dryness, foot pain, rash and dermatitis.

[Slide.]

Metabolic and Endocrine adverse events that occurred in the trials: hypertriglyceridemia did occur, and there was a significant difference between tazarotene and placebo. And I will show

you a slide concerning that.

There was also one incident of hypertriglyceridemia leading to pancreatitis, and this occurred in one patient in the placebo-controlled trials. The patient did come into the trial with severe hypertriglyceridemia, having a baseline value of about 6 mmol/L. The data was presented in millimoles per liter. And I'll talk about the conversion later--and then his triglycerides continued to rise to about 13 mmol/L, and then the patient was taken off the drug. And about a week later, his triglycerides about 33 mmol/L and 62 mmol/L, and he was worked up--had ERCP, and was found to have pancreatitis, probably due to drug product.

The applicant found hyperglycemia, a statistical difference.

There were also four cases of hypothyroidism diagnosed; three in the placebo-controlled trials, one in the long-term trial, and all the patients were on tazarotene. And I must say that even though when you looked at

TSH values in the placebo-controlled trials, you really didn't see a difference between tazarotene and placebo, as there were 2.9 percent of patients who had elevated TSH on tazarotene, and there were 2.5 percent of patients who had elevated TSH on placebo, yet the investigators did diagnose three patients with hypothyroidism.

When I went back and looked at the case report forms to see was there some other criterion that had been used to diagnose these patients outside of an elevated TSH, there had not been.

Elevated LFTs leading to discontinuation--there was one patient in the placebo-controlled trials, and this was a patient who also had an elevated TSH and had been diagnosed with hypothyroidism.

[Slide.]

Now, here is a table on elevated serum triglycerides, and these are all patients in the placebo-controlled trials--all comers. And what I did was look through the line listings, and took any patient who had a serum triglyceride that was

2.3mmol/L or greater, and 2.3 millimoles is about 200 mg/dL. And I base that on the fact that most physicians would have some type of therapeutic intervention once your triglycerides start to rise about 200--even though we all know that even as high as 130 would be considered mildly elevated, but not necessitate treatment. And moderate--2.8 to 5.6 millimoles which--it's about 250 to 500 mg/dL, and greater than 5.61 is anything higher than that.

And just for your information, if you're greater than 11 mmol/L, then that's about greater than 1,000 mg/dL. And there were maybe a couple of patients who got up as high as 750 mg/dL.

And, at any rate, there are about 45.2 percent of patients in the 048 trial, and 42.3 percent in the 050--049--trial, that had elevated serum triglycerides on at least two occasions during treatment. And compared to placebo, this was found to be statistically significant.

[Slide.]

In the post-treatment period for the

placebo-controlled trials, only cheilitis remained a statistically significant event. Skin and appendages as a whole was also considered statistically significant, but that was driven primarily by dry skin, which is not something unexpected from an oral retinoid. And I will say that the serum triglycerides returned to acceptable range in about 55 percent of patients followed in the post-treatment period; that is, those patients who I just previously talked about who had elevated triglycerides, if they were followed in the post-treatment period, 55 percent of them did return to an acceptable range.

[Slide.]

In the short-term open-label trial, there were a few significant adverse events in patients who were taking their second course of oral tazarotene, compared to those taking their first course; and that included arthralgias, back pain and alopecia. And, again, the first percentage--like 33.7 percent--is for the patients taking their second course of tazarotene,

versus--for example, in the arthralgias--the 14.1 percent of patients who had arthralgia taking their first course of tazarotene. And alopecia again emerged as a new adverse event.

And significant laboratory abnormalities in the short-term trial for patients who were taking the second course of tazarotene included elevated serum triglycerides, as in the placebo-controlled trial, and also now elevated alkaline phosphatase levels.

[Slide.]

In the long-term open safety trial, one or more adverse events were reported for 98.9 percent of the patients. And adverse events that occurred for greater than 5 percent of the patients, again, are cheilitis, arthralgia, myalgia, infection dry skin--

[Slide.]

--back pain, headache, asthenia, pruritus, foot pain, alopecia, leg pain and arthritis--

[Slide.]

along with paresthesia, flu syndrome,

nausea, joint disorder, insomnia, rhinitis and bronchitis. And most of these events were reported as mild in severity.

[Slide.]

Laboratory adverse events that occurred in the long-term safety trial--which, again, is the 52-week trial--included hypertriglyceridemia, again, at 41.1 percent, which sort of paralleled the placebo-controlled trial. And, again, these are patients who had elevation at least on two time points during treatment, and their elevations were greater than 200mg/dL; abnormal liver function tests in 22.9 percent; elevated CPK in 16.3 percent; elevated alk-phos, 13.7 percent; and isolated elevated SGPT and SGOT--because some patients just had one or the other; abnormalities in white blood cell counts, 5.7; and elevated GSH, 5.3 percent.

[Slide.]

And out of all of that, the higher elevation--the alkaline phosphatase is something to focus on a little bit. There was a higher elevation

compared to placebo-controlled trials in the long-term study: 13.7 percent of patients versus 3.4 percent of patients in the placebo-controlled trials, suggesting that the longer you're on the drug, that there's some effect there to alkaline phosphatase.

And, again, it remained elevated at the end of the post-treatment period, which was a 12-week post treatment period, in 69.4 percent of those patients who were abnormal.

Only 3.7 percent--or 2 out of 54 patients who had elevated LFTs had abnormalities in their liver function tests at the end of the post-treatment period, suggesting that there may be a bone origin for the elevation of the alkaline phosphatase values.

[Slide.]

And this kind of takes us to the effects that were found on bone metabolism in the clinical trials. And I should preface this by saying we had a consultant at the agency look at the data. And there is a high drop-out rate, and missing data, in

the long-term trials. And so it's hard to make a definitive conclusion. And more studies and a more long-term look at its effect--at tazarotene's effect over long term might really be necessary.

But what was found was that there was a mean bone mineral density decrease over time for the entire set of patients, with some having decreases close to 30 percent. And over 10 percent had significant decreases of greater than 5 percent. And four patients on tazarotene, and one on placebo, had bone marrow density decreases greater than 5 percent in the placebo-controlled trials. And this occurred in men--all of them were men, in the range of 40 years old to 69 years of age. And one patient also had a decrease of 50 percent in bone marrow density, and that's still being investigated.

But we feel that this might be significant because men, who composed the bulk of the study--and there were 68 percent of men in the long-term trial, and over two-thirds of men in the placebo-controlled trials--those patients usually lose bone mineral

density at about 0.5 to 0.75 percent per year, and women usually lose about 1.5 to 2 percent per year. That's a lose of either 1 to 3 percent over a 36 weeks supplies a greater than normal bone loss over a year. And so, over a period of five to 10 years of treatment, this really could be significant.

[Slide.]

In the long-term study, 5.3 percent of patients had significant changes in calcification and/or osteophyte scores of the cervical spine; 26 percent had worsening changes in hyperostosis and ligament calcification with each vertebrae of the cervical spine; and there was a significant increase in ankle ligament osteophyte formation at weeks 52 and 64.

[Slide.]

And this correlates to the musculoskeletal adverse events that also increased in the long term trial. And in the post-treatment period these adverse events remained significant; arthralgia, at 19.7 percent; back pain, 17.8 percent; myalgia, 15.8 percent; and arthritis at 6.6 percent.

There were also six moderate fractures occurring during the trials in patients on tazarotene that were reported as "without known cause," and we're still having that investigated.

[Slide.]

And other adverse events that occurred in the post-treatment period of the oral tazarotene trial are as expected with oral retinoids: cheilitis, dry skin, asthenia and pruritus.

[Slide.]

Discontinuations due to neuropsychiatric events--in the placebo-controlled trials, due to emotional lability, there were three patients on tazarotene and three patients on placebo who discontinued. For depression, there was one patient on tazarotene and none on placebo.

And in the open-label trials, two patients discontinued for depression, five patients for emotional lability, and one patient discontinued secondary to a paranoid reaction.

[Slide.]

The conclusions that we can make from this

for neuropsychiatric events is that there is no difference between tazarotene and placebo in the controlled trials, for neuropsychiatric events. However, due to the limitations of the metrics employed and the statistical power, an association cannot be ruled out, given the existing concerns about such effects from other retinoids.

[Slide.]

And ophthalmology--we looked at--used several metrics to looked for ophthalmologic effects secondary to tazarotene. And those employed were visual acuity, biomicroscopy and opthalmoscopy, and no signal was detected.

[Slide.]

As stated earlier by Dr. Walker, there were four pregnancies in the trials for oral tazarotene; one in the psoriasis trial, and three in the acne trials. There were two elective abortions, one spontaneous abortion, and one term delivery at 38 weeks. And, as she said, they have later follow-up that, so far, this child appears normal.

[Slide.]

Now I'm just going to switch over to the efficacy portion, and just give you a brief description of the trials--you've already heard about this earlier today.

There were two Phase 3 efficacy trials, which were identical in design. They were multicentered, randomized, evidence-based and placebo-controlled. The patients took either tazarotene as a 4.5 capsule or its placebo once a day for 12 weeks. And there was a 12-week post-treatment follow-up.

[Slide.]

The key inclusion criteria included that the patients had to be age 21 years or older. They had to have a severity score of greater than or equal to 3, which was "moderate" on the Overall Lesional Scale.

They also had to a minimum surface area involvement of 10 percent.

[Slide.]

Key exclusion criteria included:

spontaneously improving or rapidly deteriorating plaque psoriasis; any patient with a previous fracture, anomaly, or artifact of the ankles or cervical spine; use of systemic retinoids within eight weeks prior to study entry; use of systemic medications known to affect bone within 12 months prior to study entry.

[Slide.]

Also, patients with suicidal ideation were excluded; females of childbearing potential who were unable or unwilling to use two birth control methods at the same time during the 28 days prior to the week-zero visit and during the treatment and post-treatment periods of the study; and also any male who was unwilling to wear a condom when having sexual intercourse with a female of childbearing potential during the study was also excluded.

[Slide.]

The efficacy variables, as determined by the FDA--and what we based our efficacy assessment on--included: one primary efficacy variable, and that was the Overall Lesional Assessment Score, and

this varied from "0" with no disease, to "5" with very severe disease.

The secondary efficacy variables, which were supportive of the primary, included the clinical signs of psoriatic lesions, the erythema, scale and plaque elevation, and overall global response.

[Slide.]

Treatment success for the efficacy in pivotal trials was defined as success being a score of 0 or 1--meaning "none" or "minimal disease" on the OLA scale at week 12--at end of treatment.

And now Dr. Shiowjen Lee is going to speak to you about the efficacy results.

Efficacy-Biostatistical Analysis of Pivotal Studies

DR. LEE: Good morning. In the next 30 minutes I will be presenting you the biostatistical analysis of pivotal studies.

[Slide.]

The efficacy evaluation of the two pivotal studies included the following efficacy endpoints: primary efficacy endpoint--treatment success--which

is defined as percentage of patients with Overall Lesional Assessment--abbreviated as OLA--score of 0 or 1 at week 12, which has the disease of "none" or "minimal."

The secondary efficacy endpoint included clinical signs and symptoms, and overall global response. The overall global response measures the overall improvement from baseline about the disease status. And Dr. Denise Cook will have comments about this efficacy endpoint later.

And other efficacy end point, we are particularly interested in the scalp and nail psoriasis.

In this presentation, I will focus on the primary efficacy endpoint and the scalp and nail psoriasis end point.

[Slide.]

Presentation of the efficacy findings in two pivotal studies are organized by the following. First, I will present you the overall efficacy findings of oral tazarotene versus placebo, and next I will present to you the subgroup efficacy

results, in particular, by gender and by baseline OLA severity score. Next, I will show you the short-term efficacy of oral tazarotene in treating the scalp and the nail psoriasis. And, next, I will give you the relapse rate--it's referred to the short-term relapse rate for the two pivotal studies.

[Slide.]

This table gives you the baseline demographics for the two studies; in particular, I listed gender and OLA score.

For patients treated with tazarotene in the first study, we enrolled 166 patents. And among those 166 patients, 80 percent of them male, and 20 percent female.

In the first study, enrolled 171 patients in placebo group. And in the placebo group the patients were 72 percent male and 28 percent female.

For the second studies, the study enrollment enrolled 182 patients in tazarotene, and 187 patients in placebo. For patients assigned

with tazarotene treatment, 65 percent male, and 35 percent female; and for placebo groups, 74 percent male, and 26 percent female.

And I want to point out here, in the two pivotal studies, the male patients accounted for over two-thirds of study enrollment.

With respect to the baseline OLA score, most patients had a moderate disease severity, where they can enter the study. For example, in the first study, patients with tazarotene group, we have 60 percent patients had a moderate disease severity. And for the second studies, there was 66 percent patients had a moderate disease severity.

And I want to point out here, in the first study there were total of five patients in the very sever OLA score at baseline. And two of them treated with tazarotene. And in the second study we have total 10 patients in the second study, and four of them treated with tazarotene. And the total patients with very severe disease severity at baseline was 15 patients, and accounted for about only 2 percent of patient enrollment.

[Slide.]

This table gives you the efficacy results about the OLA score and the treatment success at week 12.

For the first study, the treatment success rate were 15.7 percent for tazarotene group, and 3.5 percent for placebo group. And for the second study, the success rates were 18.7 percent for tazarotene group, and 4.8 percent for placebo group.

There are two--I would like to make a point here. The first point is the treatment success for both studies, they are under 20 percent. And, also, the most patients with treatment success, they had a score, primary would be 1. For example, in the first study, patients treated with tazarotene, we have 22 out of 26 patients had a score of 1. For the second study, we have 27 out of 34 patients had a score of 1.

[Slide.]

This slide gives you the subgroup results of treatment success for the first study, primarily

by gender and by baseline OLA score. Recall, the overall success rates were 15.7 percent for tazarotene, and 3.5 percent for placebo.

For gender, female patients generally had higher success rate than males. And here we have, in tazarotene group, female success rate was 26 percent, and the male success rate was 13 percent.

With respect to the baseline OLA score, generally the success rate decreases as the baseline disease severity increases. For example in tazarotene group we have 19 percent success rate for patients with moderate disease severity, to 11 percent with severe disease severity at baseline, and to 0 percent for patients with very severe disease status at baseline.

[Slide.]

And this slide gives you the subgroup results of treatment study. The overall success rate for the second studies were 18.7 percent for tazarotene, and 4.8 percent for placebo. And here, again, are listed by gender and by baseline OLA score. For female subjects, again, higher success

rate than male subjects. And here, I want to point out, the treatment difference for female patients in this study is about 9 percent. This is 24 percent minus 15 percent in 9 percent. And for male subjects we had 16 percent in tazarotene group--success rate--and the placebo group 1 percent. The treatment difference here was 15 percent.

And one might question about the efficacy results driven by male subjects, because it has larger size of treatment difference. Because, again, over two-thirds of patient enrollment will be males. We've done some sensitivity analysis for this, and it's shown the tazarotene group still superior to placebo, however, the bigger size difference does have an impact of the significance level of superiority.

With respect to the baseline OLA score, disease severity increases then the success rate decreases; from 20 percent for patients with moderate disease, to the last category--very severe disease--and with 0 percent success rate.

And I want to point out here, even patients from the previous study, and for this second study, none of the patients in tazarotene group achieved treatment success for patients with very severe disease status.

[Slide.]

The next I'm going to discuss with you about the scalp and nail psoriasis. The evaluation of scalp and nail psoriasis is based on short-term efficacy of tazarotene treatment. And the severity of each scalp, fingernail, toenail psoriasis was evaluated based on a 5-point scale; 0 was "no disease," and score of 4 was "very severe" disease.

[Slide.]

The efficacy results presents you--the next slide--is based on the percentage of patients having severity score of 0 at week 12.

This table gives you the results about the scalp and nail psoriasis, with respect to the patients with severity score of 0 at week 12.

As you can see, for the two studies, with respect to the scalp psoriasis, there was 27

percent patients in tazarotene group had a severity score of 0 at week 12. And for the placebo, there was 7 percent in the first study, and 12 percent in the second study. So, tazarotene shows some efficacy in treating scalp psoriasis.

However, if you take a look at the fingernail and the toenail, no patient in tazarotene group had a severity score of 0 at week 12. However, you take a look at the toenail in placebo group, there was one patient achieved severity score of 0 at week 12, and there were two patients in the second study achieved a severity score of 0 at week 12 for fingernail psoriasis.

And I want to point out here is 12 weeks might be too short for evaluating nail psoriasis, as nail growth requires longer period of time to grow.

[Slide.]

The results going to present you here is baseline of patients who were treatment success at week 22, and had a relapse during the 12 week post-treatment.

Two definitions of relapse are considered in this presentation. The first definition is based on patients who fell back to baseline OLA score or worse during the 12-week post-treatment period.

The second definition is based on patients whose achieved maximal improvement from baseline was reduced by more than 40 percent during the 12 weeks post treatment.

[Slide.]

This slide gives you the results about the relapse rate for the two pivotal studies. As you recall, there were 26 patients in tazarotene group, and six patients in placebo group had treatment success at week 12 for the first study, and 34 patients in tazarotene group and nine patients in placebo group achieved treatment success in the second study.

Based on the first definition--"a"--which includes the patients who fell back to the overall--the "OLA score at baseline or worse, the relapse rate for tazarotene group in the first

study was 23 percent, and it was 9 percent for the second study.

Based on the definition "b," which includes patients whose maximal improvement was reduced by more than 50 percent, in tazarotene group we have 35 percent relapse rate for the first study, and 26 percent relapse rate for the second study.

The next several slides, I'm going to give you the summary of the statistical analysis in the two pivotal studies--basically, just summarize the results I just presented you.

[Slide.]

Oral tazarotene is statistically superior to placebo regarding treatment success, however success rates are below 20 percent for both studies; one was 15.7 percent, the other one is 18.7 percent.

Female patients generally had higher success rates than males. The male patients in the two pivotal studies accounted for over two-thirds of study enrollments.

Treatment success decreases as baseline disease severity increases. It should be noted a total of 15 patients, which accounted for about 2 percent of study enrollment, had a "very severe" OLA score at baseline. None in oral tazarotene group achieved treatment success at week 12. Consequently, there is insufficient data to evaluate the efficacy claim of "very severe" plaque psoriasis.

[Slide.]

Oral tazarotene demonstrates short-term efficacy in treating scalp psoriasis, but not nail psoriasis. Two and one patients in placebo group achieved severity score of 0 at week 12 in fingernail and toenail psoriasis, respectively. However, none was in oral tazarotene group.

[Slide.]

Based on definition (a) of relapse, which is the patients who fell back to OLA score at baseline or worse, the relapse rate was approximately 15 percent for both studies. And based on definition (b), which includes patients

whose maximal improvement from baseline was reduced by more than 50 percent, the relapse rate was 30 percent for the two pivotal studies. And, again, the relapse rate was measured based on patients who had a treatment success at week 12, and they had relapsed at the 12-week post-treatment period.

This is the end of my presentation.

Thank you.

Clinical Wrap Up

DR. COOK: Okay, I'm back [laughs]--I'm back for, hopefully, the last time. And I'm just going to try to give a clinical wrap-up. And, basically, this is to give you other information on the safety and efficacy of the chemical moiety tazarotene.

[Slide.]

I'm going to speak about drug-use trends of topical tazarotene, adverse events with topical tazarotene, and we'll take a look at the efficacy of topical tazarotene and, again, of oral tazarotene.

[Slide.]

Drug-use trends for topical tazarotene--the total number of tazarotene prescriptions have been increasing. In 1999, there were 226,000 prescriptions written, and in 2003, there were 937,000 prescriptions written.

In 2003, most of the prescriptions were prescribed by dermatologists--67 percent--with family practitioners coming in at 7 percent. And the most common diagnoses associated with the use of topical tazarotene was 75 percent for acne, and 13 percent for psoriasis.

[Slide.]

58 percent of all of the prescriptions were dispense to women. And we arbitrarily chose 12 to 44 years as the most common range for women of childbearing potential, and 46.5 percent of all claims are for women of childbearing potential.

[Slide.]

There have been 125 errors reports associated with topical tazarotene--adverse event reports. And the most common adverse events are cutaneous: pruritus, rash, dermatitis exfoliative,

burning sensation, and erythema.

There are also some systemic adverse events reported with the use of topical tazarotene. There are three reports of elevated LFTs, gastrointestinal problems; hot flashes and perspiration; and one report of elevated triglycerides.

The indications for which the prescription had been written included 91 for psoriasis, eight for acne, other skin 10, and for the others we don't have the diagnosis.

There were more females--69 females and 52 males--for which these adverse events were reported, and there were two hospitalizations, and one congenital anomaly.

[Slide.]

The association with pregnancy exposures--there have been 113 worldwide pregnancy exposures-- and this data was actually obtained from the sponsor.

There are 107 reports in the United States, compared with six foreign reports. The age

range was 17 to 38 years, the median being 29 years. The indications for which these prescriptions in these exposures had been written were primarily acne--60; 20 for psoriasis; two for facial wrinkling; and the others, we don't know.

And the outcomes for pregnancy, and fetal outcomes: there were four spontaneous abortions, two chromosomal abnormalities--trisomy 18 and Cornelia de Lange--not associated with retinoid malformations. And the others--107--there was either no adverse outcome or unknown. And we don't know how many of which of those two categories compose the 107.

[Slide.]

And finally we're going to take a look at the efficacy of the chemical moiety in the treatment of plaque psoriasis.

In topical tazarotene, in the clinical trials, the success was based on a greater than 75 percent improvement. And I have to preface this by saying that we know that these are different trials, these are different sets of patients. They

all had moderate to severe psoriasis.

With the 0.05 percent gel, the success rate was 30 percent and 18 percent in the two clinical trials. The 0.1 percent gel, the success rate was 38 percent and 25 percent, compared with a placebo effect of 13 percent and 10 percent.

If you look at oral tazarotene, which we've been speaking on today, in the clinical trials the success was "no" or "minimal disease," which is a more stringent criterion, and the success rate was 15.2 percent, and 18.7 percent, respectively, with a lower placebo effect.

Also, in the clinical trials on oral tazarotene, a secondary efficacy parameter was the global response. And a success of greater than or equal to 75 percent improvement, or marked improvement or better--which Dr. Walker showed you earlier--showed that this success rate was 30.1 percent, and 30.8 percent, with a placebo effect of 8.2 percent and 9.1 percent.

So, in summary, in pre-clinical animal studies, oral tazarotene, when compared milligram

for milligram to other systemic retinoids turns out to be the most potent teratogen. Thus, as the other retinoids are human teratogens, oral tazarotene is most likely a potent human teratogen.

While it is true that oral tazarotene showed efficacy as compared to placebo in the treatment of moderate to severe psoriasis, given the safety signals discussed today, in presence in semen, its effects on lipid metabolism, bone metabolism and thyroid and glucose metabolism, oral tazarotene presents a complex risk-benefit calculus.

We at the agency look forward to the guidance of this advisory committee in analyzing this complex drug product.

Thank you.

DR. STERN: I'd like to thank the FDA for its very nice and lucid presentations, and we'll now go on to Dr. Lindstrom, who will talk about the evaluation of risk management for systemic retinoids in a more generic way.

Evolution of Risk Management for Systemic Retinoids

DR. LINDSTROM: Good morning. I'd like to discuss with you today the evolution of agency thought regarding pregnancy prevention risk management for systemic retinoids for skin conditions.

[Slide.]

To accomplish this, I'll first describe the current landscape in terms of retinoids on the market for cutaneous conditions; the risks that they present; and the risk-management tools available to us. I'll then move on to describe the historical development of risk management for systemic retinoids for cutaneous conditions. And, finally, I'll make a few summary remarks.

[Slide.]

There are four systemic retinoids approved for the treatment of cutaneous conditions. Isotretinoin is indicated for the treatment of severe, recalcitrant nodular acne. The innovative product was approved in 1982, and three generic products were more recently introduced.

Etretinate, indicated for the treatment of

severe recalcitrant psoriasis was approved in 1986, and this product was voluntarily removed from the market in 2002.

Acitretin, with a similar indication, was approved in 1996, and bexarotine, indicated for the treatment of refractory cutaneous T cell lymphoma was approved in 1999.

[Slide.]

Now, all of the approved systemic retinoids are either recognized, or highly suspect human teratogens, and all produce fetal abnormalities in animals that are exposed in utero.

We have the most human data for isotretinoin, which is recognized as a potent human teratogen. It has a high frequency of adverse outcomes in exposed pregnancies, with perhaps a third of exposed pregnancies affected. The effects are severe, including fetal wastage, structural malformations in major organ systems, and impaired function, such as neuropsychiatric delay.

Additionally, the window of vulnerability is large. There's no recognized time period during

gestation when administration of systemic retinoids would be considered safe.

[Slide.]

Considering that risk, what risk-management tools are available to us? Well, we broadly categorize our risk-management tools into four groups: product labeling, such as the package insert; targeted education--an example would be patient brochures, reminder systems, such as stickers or patient informed-consent forms; and controlled distribution.

[Slide.]

I want to move now to describe the history of pregnancy prevention risk-management efforts. I'm going to use isotretinoin as a prototype, and use three other oral retinoids as supplementary examples. Before I do so, I want to acknowledge a caveat that Dr. Walker has already discussed, and that is that isotretinoin is indicated for the treatment of severe acne. This is different than the indication that oral tazarotene is pursuing. And when isotretinoin is prescribed for severe

acne, it's prescribed as a circumscribed 20-week course, and the majority of patients will experience prolonged or permanent disease remission--not all, but the majority--and will likely require a single course of therapy.

However, the other retinoids that I will use as supplementary examples--etretinate, acitretin, and bexarotine--are prescribed in a chronic, or chronic-intermittent fashion, and would not be considered--or the use would be more similar to that which might be expected for oral tazarotene

[Slide.]

Isotretinoin was approved--as I've mentioned--for the treatment of severe recalcitrant nodular acne in the early '80s. It was recognized as a highly suspect teratogen, based on abnormalities seen in animal studies. It received a pregnancy category rating of X, and when it was released to the market, risk management included labeling, information regarding the potential risk for teratogenicity was included in the contraindications, warnings and precautions section

of the label.

[Slide.]

Despite this, the agency received the first report of a human malformation following in utero exposure to isotretinoin in 1983, and other reports followed soon after.

In response, the labeling was strengthened. First, the teratogenicity risk information already included in the package insert was highlighted by boldface type, and a boxed warning was added at the beginning of the label. In addition, targeted education tools included "Dear Doctor" and "Dear Pharmacist letters, which were sent out to health care providers to update them on the human data as it accrued.

[Slide.]

But, again, additional exposures--in utero exposures--occurred, and in 1988, the agency and the sponsor both determined that strengthening of the risk-management program--pregnancy prevention risk-management program for acitretin was needed. And after consultation and input from the advisory

committee, the Accutane Pregnancy Prevention Program was introduced. It included tools from three of the four categories of risk-management tools.

The labeling was updated. The boxed warning was updated to include additional information regarding the timing and frequency of pregnancy testing; the number and types of contraception recommended; and the recommended duration for their use.

Additionally, the package itself was changed. The blister pack was introduced. The "Avoid pregnancy" icon--the familiar red-circle with the slash was introduced, and the boxed warning, which had previously been just on the package insert was now printed on the package itself.

[Slide.]

Other components of the Accutane Pregnancy Prevention Program included educational materials for physicians--excuse me, for prescribers and patients, as well as the introduction of a referral

and reimbursement program for contraceptive counseling, as well as an informed consent form for female patients.

Two other components of the Accutane Pregnancy Prevention Program, not formal risk-management tools in themselves, are the patient survey and the prescriber survey, both of which were introduced to assess the impact of the program.

And what was the impact?

[Slide.]

In the first year after implementation, we saw an initial rise in the number of reported pregnancies--reported exposed pregnancies. This was not surprising, as a new tool for reporting--the voluntary patient survey--had been introduced. However, in the subsequent decade, this number--the number of reported exposed pregnancies--leveled off and stayed relatively constant.

Also during this time, the number of patients treated with isotretinoin doubled. Now,

it might be tempting to conclude, having said that the number of reported exposed pregnancies was relatively constant, and the number of prescriptions and the number of patients treated was rising, it might be tempting to conclude that the pregnancy rate was dropping.

This would be an erroneous conclusion because the number of reported pregnancies--pregnancy reporting is voluntary, and the number of reported exposed pregnancies does not necessarily represent all exposed pregnancies. And we do know that adverse event reporting falls off over time.

However, we can safely say--I think we can safely conclude that the known total public health burden of exposed pregnancies was not decreasing, and the number of women at risk for exposure during pregnancy was increasing.

[Slide.]

Because of these two issues, the Dermatologic and Ophthalmic Drug Advisory Committee was convened in 2000, and this advisory committee

recommended that the isotretinoin risk-management plan at the time--the Accutane Pregnancy Prevention Plan--be strengthened to include registration--mandatory registration and controlled distribution.

Now, there was a precedent for the committee's recommendation, in that Thalidomide, which was reintroduced to the U.S. market in 1999, was introduced with a risk-management plan that contained these elements of registration and controlled distribution.

After the advisory committee, the agency and the sponsor entered into intense negotiations, and in 2002 the current risk-management plan was implemented.

Now, the innovator sponsor entitled that program the SMART program--the System to Management Accutane-Related Teratogenicity. The generic manufacturers which entered the market soon after that, gave their risk-management plan--which was identical in all of the essential elements--different acronyms: SPIRIT, ALERT,

IMPART. In order to avoid confusion, I'm going to refer to all of them as the "current risk-management plan." Although it is being revised, it is the risk-management program that is in place at the present.

[Slide.]

Its components included elements for all four categories of risk-management tools. The labeling was updated, and a medication guide was added. There were instruction guides for prescribers and pharmacists; brochures for patients.

[Slide.]

The patient informed-consent forms were updated. There was a prescriber checklist to assist prescribers in implementation of this risk-management plan. Perhaps the hub of the plan was the yellow qualification stickers. These yellow stickers are applied by prescribers to prescriptions when they write them for isotretinoin. There's a place to write the date on which the patient has been qualified.

Qualification entails ensuring that the patient has had a recent negative pregnancy test, and that the patient has agreed to use two forms of effective contraception--unless that patient is abstinent, post-menopausal, or male.

Also on the yellow qualification sticker are reminders for pharmacists to dispense only a 30 day supply, not to give refills, and to fill the prescription within seven days of the qualification date.

Now, these qualification stickers are obtained by prescribers by signing a letter of understanding in which they attest that they possess the relevant competencies necessary to safely prescribe isotretinoin and that they agree to fully utilize the risk-management program. The yellow stickers are provided by the sponsor upon receipt of the signed letter of understanding.

The voluntary patient survey and pharmacy surveys--again, not risk-management tools in themselves--were used to assess the impact of the program. And at the time of approval of the

program, the sponsor was informed that the effectiveness would be assessed at one year, and performance benchmarks were set at a patient survey enrollment of 60 percent, and qualification sticker use approaching 100 percent.

[Slide.]

The one year metrics were presented to this combined advisory committee in some detail in February of this year. And I'm just going to summarize them with a single slide.

The patient survey response rate was 36 percent. It failed to meet the sponsor-identified benchmark of 60 percent.

Sicker use was high, exceeding 90 percent, but it proved to be an unsatisfactory surrogate endpoint, in that there was poor correlation between sticker use and survey responses. For instance, although, again, the sticker use was high and above 90 percent of the stickers were correctly filled out, a significant number of women on the voluntary survey did not recall having received any pregnancy test. And perhaps most importantly, the

number of reported exposed pregnancies was unchanged after implementation of the current risk-management plan from the previous year.

[Slide.]

And so, this combined advisory committee recommended, in February of this year, that the current risk-management plan be augmented, and specifically, your recommendations included: mandatory registration of all patients, both male and female; registration of all pharmacies; registration of all prescribers; and the implementation of mandatory pregnancy registry. And I want to inform you that the sponsors and the agency are diligently working to implement these recommendations.

[Slide.]

So, a quick review of the isotretinoin risk-management program chronology: the drug was approved in 1982. In 1988 the Accutane Pregnancy Prevention Program was implemented. In 2002 the current risk-management program was implemented. And in 2004, this combined advisory committee

recommended mandatory registration, pregnancy registry, and controlled distribution.

I want to discuss three other systemic retinoids at this time.

[Slide.]

Etretinate was the second oral retinoid approved in the United States. It was approved in 1986 for the treatment of severe recalcitrant psoriasis. It was approved after isotretinoin entered the market, but prior to the implementation of the Accutane Pregnancy Prevention Program. And the risk-management program for etretinate included--was limited to labeling, with a boxed warnings and warnings regarding the risk of teratogenicity in the "Warnings, Contraindications and Precautions" section of the label. And, as I've mentioned previously, this drug was withdrawn from the U.S. market in 2002.

[Slide.]

Acitretin--the third oral retinoid approved for the treatment of a cutaneous condition, was approved in 1996 for the indication

of severe psoriasis. There is a caveat in the indications section, indicating that in women of childbearing potential this drug should be used only if they are unresponsive to other therapies, or if other systemic therapies are contraindicated.

[Slide.]

Acitretin was approved, as I said, in 1996. This was after the implementation of the Accutane Pregnancy Prevention Program, and hence the sponsor was asked to implement a risk-management program that was consistent with the best practices at that time.

The sponsor labeled their risk-management program for Soriatane, the "Soriatane Pregnancy Prevention Program," and it contained elements similar to the Accutane Pregnancy Prevention Program: labeling, education and reminders.

Targretin--bexarotine--was approved in 1999, the fourth oral retinoid to treat a cutaneous condition. It's indicated for the treatment of the cutaneous manifestations of cutaneous T cell lymphoma which is refractory to other system

therapies. And--again, approved in 1999, this would have been after the implementation of the Accutane Pregnancy Prevention Program, but before the implementation of the current risk-management program. And the risk-management program for bexarotine is similar to that for--it's similar to the Accutane and Soriatane pregnancy prevention programs. It consists of labeling, targeted education, and a limitation on the amount dispensed to 30-day supply.

[Slide.]

I just want to conclude with a few summary remarks.

All of these approved systemic retinoids are known or highly suspect human teratogens and, as such, present potential risks to the public health that needs to be management. Risk-management programs should incorporate current best known practices, and these practices for pregnancy prevention risk management have evolved over time, and have progressively included elements from the four categories of risk-management tools:

labeling, targeted education, reminder systems, and controlled discrimination.

[Slide.]

And our current thinking regarding best practices for pregnancy prevention risk management for isotretinoin include the fact that per the advice of this combined committee, the isotretinoin current risk-management program needs to be strengthened, and that elements--and that that strengthened program should include the following elements: mandatory registration of patients, prescribers and pharmacies, as well as a mandatory pregnancy registry.

And I now want to turn the microphone over to Dr. Ann Trontell from the Office of Drug Safety, who will discuss risk-management tools for oral tazarotene.

Risk Management Tools for Oral Tazarotene: Context, Considerations and Experience

DR. TRONTELL: Good morning.

I'm going to hope to set some context, as well as describe considerations that FDA has taken

into account, as well as our experience in risk management, and in particular in the context of potential risk management tools for oral tazarotene.

[Slide.]

I'm going to set the context in terms of the recently issued draft guidances on risk management, from the agency. I'll talk about our experience with application of some of the tools of risk management, and what we know of their advantages and disadvantages.

I'll talk briefly about the isotretinoin rm

program. Dr. Lindstrom has already told you quite a bit. I'll talk somewhat about he ongoing negotiations. And then I will talk about the options for risk management for tazarotene which, in fact, have changed since these slides were prepared.

[Slide.]

As many of you know, under the third reauthorization of the Prescription Drug User Fee

Act, the agency was charged with developing three interrelated guidances on the topic of risk management. The first dealt with premarketing risk assessment; the second, with pharmacovigilance and pharmacoepidemiology--largely applied to the post-marking setting; and the third document now discusses what we term "risk minimization action plans"--a term that you've heard this morning. I'll use that, as well as "RiskMAPs" interchangeably.

[Slide.]

In this guidance, a risk minimization action plan--or RiskMAP--was defined as a strategic safety program designed to meet specific goals and objectives in minimizing known risks of drug products. In this context, a RiskMAP is described as a program that goes beyond what FDA usually does in the approval of a drug product. Ordinarily FDA, and with the sponsor, develop professional labeling and then conduct routine postmarking pharmacovigilance. And this largely constitutes sufficient risk management for most marketed drug

products.

[Slide.]

For risk minimization action plans the goals are described as targeting the achievement of a health outcome related to the known risks of the product. These goals would reflect the idea outcome of the RiskMAP; that might be achievement of a certain health outcome, or avoidance of an undesirable health outcome.

FDA recommends that these be stated in absolute terms to maximally reduce the risk. So, in the case of teratogenicity risk reduction, the goal might well be stated as "no fetal exposure should occur.'

Foals are broken down into intermediate steps that are also termed "objectives." And it's in the context of objectives that we talk about RiskMAP tools.

[Slide.]

These are processes or systems intended to minimize known safety risks, and are designed to target the achievement of at least one or more

objectives that serve the overall RiskMAP goal.

[Slide.]

In its draft guidance issued in May on RiskMAPs, FDA set forth a number of different considerations an how tools might be selected. Each tool, ideally, should be adding value in attaining the program goals. They should seek, wherever possible, to use tools that have proven effectiveness, either in other programs, or based upon the scientific literature.

FDA also advocates that the tools chosen be acceptable to a wide range of audiences, and certainly those individuals who will participate in the implementation of the plan, and low burden should be a goal for that, as well.

The agency suggested that in selecting risk-management tools, that one avoid unnecessary limitations on product access, since that might restrain or constrain benefits of the product, and to similarly avoid the creation of multiple customized tools, since this creates confusion as well as burden on the health care system. And,

again, so far as one is able to anticipate unanticipated consequences of a risk-management program, those should be considered.

[Slide.]

In the draft guidance, FDA describes three broad categories of tools that can be used for purposes of risk minimization--some of these have been described already by Dr. Lindstrom--the first being targeted education and outreach; this involving educational materials that go beyond the professional labeling, and may be targeted to health care practitioners or to patients.

The second category is what has been termed "reminder systems." This may use tools such as stickers, that were used in the isotretinoin risk-management program, or informed consent. In some instances limitations on product supply or packaging has been put in place to try and guide clinicians and patients in using products in the most appropriate and safe ways.

The third category involves a somewhat awkward terminology. It's somewhat equivalent to

the control distribution terminology that Dr. Lindstrom mentioned in her talk.

In the draft guidance FDA refers to the tool system involving limitations on distribution as "performance-linked access systems." These are programs that, in fact, do constrain availability of the product to certain conditions' being met. Often there's a selected group of individuals who may be able to prescribe, dispense or use this product. And often these are tied to mandatory performance of some of the reminder systems described in the previous category.

Some product examples may give you a better understanding of these tool categories.

[Slide.]

In the area of target education and outreach, we can't really give you a full list because there are probably, at this point, several hundred products that have either patient product inserts, or medication guides--a much smaller number in that category. Also, a number of programs employ patient brochures, various forms of

continuing education for physicians and pharmacists.

Reminder systems include the ones I list here. Alosetron, like isotretinoin, uses a sticker program that indicates that the clinician is familiar with the disease [sic], its risks and how to appropriately prescribe it to the patient in light of certain safety considerations.

For the drug product lindane, the amount of product now available to patients is limited to one or two-ounce aliquots to reduce the risks of individuals' using excessive amounts, or using it repeatedly and exposing themselves to certain toxicity. So the drug product abarelix, a product used for advanced prostatic cancer, certain constraints are placed on how that product is prescribed; in particular, to restrict it to those individuals whose disease warrants the risk of anaphylactic reactions with it.

In the category "performance-linked access systems," I have six products listed here. Bosentan, dofetilide and mifepristone are programs

that, in fact, operate under a form of specialty pharmacy distribution. There may be one, or perhaps a few handful of pharmacies where individuals are able to obtain the product. And I will apologize--I mis-spoke. The products that are under the specialty category include Bosentan, mifepristone and xyrem.

For clozapine, dofetilide and thalidomide, these are available through pharmacies that are registered, as well as the registration processes that extend to physicians and to patients. The ones that appear with an asterisk are ones where laboratory testing is part of what's required for product access.

With regard to use and non-effectiveness of the tools, we are still in the process of trying to understand more how these tools work and which are most effective.

[Slide.]

Targeted education and outreach, as I've already said, it's been used most extensively, but formal evaluation of the effectiveness of these

programs has been limited--though many obviously believe the importance of education for all manners of risk management.

Reminder systems--again, are relatively limited in their number. They've been used infrequently, and effectiveness to date has largely been untested.

For the performance-linked access systems, or ones that register various participants, these, again, have been used sparingly, and typically they've been applied to relatively small patient populations where the therapeutic options for those patients are limited. The registration process that tracks physicians, patients or pharmacists, in fact, has allowed good data capture in terms of their effectiveness. So the effectiveness of this small category of tools is high.

Let me walk through some of the advantages, again, of these three major tool categories.

[Slide.]

Targeted education and outreach has the

advantage that education is really a motherhood-and-apple-pie issue. It's very hard for anyone to discount its value, so it's generally it's very high acceptability, and relatively easy to implement in a variety of forums and media.

The benefit of education is it has no effects on product access.

A disadvantage, however, is, in fact, it's effectiveness is still largely unknown to us when it's used in isolation of other tools. And, as was described just recently in Dr. Lindstrom's talk, when it was applied in the most early form of isotretinoin in risk management, its effectiveness was low, at least in terms of pregnancy outcomes persisting.

[Slide.]

For reminder systems, advantages of these programs are that they allow some remnants of physician, pharmacist and patient autonomy. These reminders are put in place to, in fact, make it difficult [sic] for clinicians or patients to do the night thing. They allow the opportunity for

ongoing education, and the reminder of individuals on what is necessary to achieve use of the product. And relative to the category of performance-linked access systems, they're obviously less intrusive.

But we have to acknowledge, they imposed time and monetary costs on the medical care system; and that, again, their experience to date has been largely limited. And as was discussed in the February advisory committee, the experience of the isotretinoin program showed high process compliance with the program, but limited outcome effectiveness, in that pregnancy exposures persisted.

[Slide.]

For the performance-linked access systems, advantages of this is that, in fact, it does constrain use of the product to those conditions where use is considered to be most safe. The mandatory participation of such systems, in fact, allows registration of participants and the ability to better evaluate their performance. And, in fact, this has led to our understanding of their

high performance.

The nature, not only for issues of teratogenicity risk exposure in performance-linked access systems, is because they do represent an obstacle to the ready use of the drug product, they generally tend to diminish overall utilization of the drug product; and, in a sense, then if you wanted to reduce exposure of females of childbearing potential, that would be a secondary benefit.

However, you may look at limitations on access similarly as forms of disadvantages. And, certainly, limitations in access may also present limitations to patients' obtaining benefits from the drug product. Of course, there are time and financial burdens to such programs. And the risk that is certainly known to the agency is that the existence of such programs may prompt individuals to try and seek the product in less burdensome ways, and to try and obtain it illicitly, through the internet or other measures.

Gain, the experience that has been

obtained to date in the area of pregnancy prevention, through thalidomide, has largely been limited to a small population of individuals who are not of high fertility. So experience in its extension to large numbers of young, fertile women has not yet been done.

[Slide.]

In its draft guidance, FDA tries to set forth when you might use different tools, and it's somewhat of a circular argument: you use them when you need them, and perhaps when a less severe tool--or a less intrusive tool--has proven itself to be ineffective.

Targeted education and outreach might be used alone, or certainly in combination with other tools. And in those instances where product labeling and routine pharmacovigilance have shown themselves to be insufficient. And the example certainly pertains in the case of Accutane and the development of the Accutane Pregnancy Prevention Program.

[Slide.]

Reminder systems may be implemented at such times as when targeted education and outreach are insufficient, either based upon experience with other drug products, or in the specific drug product being addressed. And the example of this system would be the development of what is the SMART, SPIRIT, ALERT and so forth programs, or what Dr. Lindstrom referred to as the "current risk-management program" for isotretinoin.

[Slide.]

The performance-linked access systems are probably the category where it may be a little easier to define the products where these may be merited, since these tools are, in fact, intrusive. These are ones that we might expect would be used largely for those products that have significant or unique product benefits, but that have associated unusual risks that may include irreversible disability or death. Examples--in clozapine, the risk is of agranulocytosis. For thalidomide, again, teratogenicity and birth defects. And the isotretinoin RiskMAP, as we've discussed, is now

under active development in that arena.

[Slide.]

Let me tell you a little bit more about what's been in progress since we last met with this committee in February. Performance-linked access system is under active discussion and development by the sponsors. The details still remain somewhat undefined. They are under active development.

The plan is to have a centralized clearinghouse that would involve all prescribers, pharmacies and patients; and that this clearinghouse would be configured to assure and account for the performance of key safety features; for example, pregnancy testing.

[Slide.]

the key safety features of the new isotretinoin RiskMAP will include all three categories of tools: targeted education and outreach; reminders; and the linkage of access to the product to the performance of certain activities.

[Slide.]

For targeted education and outreach of all participants, there will be a medication guide, patient brochures, videos. And, again, education will continue for health care practitioners, including physicians and pharmacists.

Reminders will include informed consent and attestation on the part of health care practitioners. There is some discussion of ongoing patient education and risk-factor screening as part of this program.

And the linkage of access to the product to the performance of key features goes back to the clearinghouse, which involves all prescribers, pharmacies and patients--pregnancy testing will be required for the product to be prescribed, dispensed, and for the patient to receive it.

The issue of the linkage of these separate components, in fact, remains a challenge on two grounds; first, on the technology, as also for the potential concern of constraints on the product and mechanisms for doing that that have been patented.

[Slide.]

now, these slides will actually be dated, in light of the presentation you've heard this morning. We had, at the time of these slides' preparation, two earlier versions of the risk minimization action plan proposed by Allergan.

[Slide.]

Let me jump ahead--the initial one proposed was one that was similar to the existing isotretinoin risk minimization action plan in place and current, prior to February of this year, and still currently in place. This plan, at that time, exempted males, and females who were not of childbearing potential.

The subsequent development was for--of a program that had linkage of the product's access to pregnancy testing, pharmacist validation of pregnancy testing, and patients' having monthly reeducation and assessment of their knowledge and compliance with contraceptive practices for prescriptions to be obtained. That one had excluded males and females who were not of childbearing potential. And, as we've heard this

morning, that has been since modified.

[Slide.]

So, in summary, systemic retinoid risk management for the concern of teratogenicity has evolved and has been largely informed by isotretinoin over the past approximately 20 years. It has migrated from labeling alone to the use of targeted education and outreach, the use of reminder system; and, now, the active development of a performance-linked access system.[Slide.]

And the tazarotene program--again, as you've heard this morning--is now configured to be similar to what is being developed for the isotretinoin program, with the performance-linked access system; and, as the sponsors told us this morning, applied to all patients.

Thank you.

DR. STERN: Thank you very much. Might I ask one or two quick questions?

You've talked about isotretinoin. Is there any parallel development for the other now-approved retinoids? For acitretin, bexarotine,

in terms of a parallel system for performance-linked access?

Because I think each time you've talked about isotretinoin, and not mentioned those others currently labeled.

DR. TRONTELL: I'll actually refer that question to Dr. Wilkin.

DR. WILKIN: I can't speak regarding bexarotine. That's not in our division.

We do have another systemic retinoid in our division. There are no changes at this time in the risk-management program, but we have communicated our interested with the industry group that owns that product, that we do want to have this discussion; we'd like to know what the current performance is, how successful it is, and think about the need as to whether we need to upgrade their risk-management program.

DR. STERN: Could I then ask a follow-on question of someone who's an expert on risk management--is, does one believe that when dealing with agents that have similar risk profiles, and

the same dominant group of prescribers--although the patients may vary in characteristics--that programs that apply across the board are more likely to be followed? Or are multiple programs likely to be followed?

I think in your guidance there was one little thing that said one of the things the FDA wants to avoid is too much individual customization. And I'm wondering if some of that is on the basis of likelihood of good performance when you have one-size-fits-all, rather than many sizes for slightly different product.

DR. TRONTELL: At this point in time, in fact, we--I'm not sure we have any risk-management program that exactly duplicates another. Certainly, it was based upon feedback we heard from the practicing community of physicians, as well as--and probably in particular--pharmacists. Because the confusing array of manners in which a product might be presented to a pharmacist was a cause for concern.

So the idea was, in fact, to approve some

element of efficiency, memorability, and to decrease confusion in its use.

DR. STERN: One last question before lunch.

DR. SHAPIRO: I just wonder if there's a timeline about when the Accutane proposals might be implemented, and when and how evaluation of the impact might be evaluated?

DR. BULL: There is a timeline, but in terms of it being a very, very complex negotiation, involving multiple sponsors, I would say we hope to have it as soon as possible. But it's extraordinarily complex. So, I would say as soon as all of the details can be attended to, there will be something out there. But it's being actively, very vigorously worked on.

DR. STERN: I'm sure it will be as soon as possible, but the question is when that will be [laughs.]

[Laughter.]

Dr. Wilkerson--and then we will close for lunch.

DR. WILKERSON: I just had a point of

clarification with Dr. Trontell.

There was something you said about patent issues. Could you just elaborate for us what--do we have some restraints here, or something that we don't know about?

DR. TRONTELL: We--as I think everyone is aware, some of the discussion for isotretinoin was largely framed based upon the successes of the STEPS program that was put into place for thalidomide. The issue of how features of that program may or may not be applied to isotretinoin has raised the potential question of patent protection or infringement. And that is, again, among the complex issues that are being sorted out at the present time.

DR. STERN: Thank you.

We've ended almost on time, and I'd like us to start promptly at one o'clock, and we'll adjourn for lunch.

Thank you very much.

[Off the record.]

Open Public Hearing

DR. STERN: We've now come to the part of the meeting that is the open public hearing. We have three speakers who have indicated their intention to speak. Before they speak, I must read, exactly as written, the following.

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

For this reason, the 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 sponsors of any product in the pharmaceutical category under discussion at today's meetings. For example, this 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 relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I've also been informed that I may only introduce the speakers according to number. It sounds a little bit like a Seuss novel, but would Mr.--would Person One please come?

MR. WHITE: Well, since I know Dr. Krueger, the only other thing could be either Dr. Krueger or Number One. So, I guess I'm Number One.

Ladies and gentlemen, thank you very much. I'm delighted to be here this afternoon, and appreciate the opportunity to make a few remarks before this committee.

My name is Dale White and I am Vice Chairman of the Board of Trustees of the National Psoriasis Foundation. I am volunteering to be here today on behalf of the Foundation and the community

it represents, to testify in support of the drug oral tazarotene for the treatment of moderate to severe psoriasis.

As the parent of a teenage with psoriasis, I am excited about testifying today about the urgent need psoriasis patients have for additional treatment options. Thank you again for this opportunity.

[Slide.]

By way of introduction, the National Psoriasis Foundation is a leading nonprofit organization fighting to improve the quality of life of the more than 5 million Americans diagnosed with psoriasis or psoriatic arthritis.

The Foundation was established in 1968 by a grassroots network of patients and physicians.

Through education and advocacy, the Foundation promotes awareness and understanding, ensures access to treatment, and supports research that will lead to effective management of this very serious chronic disease--and, ultimately, a cure.

Each year the Foundation receives

financial support from tens of thousands of people, and from 15 to 20 pharmaceutical companies. This includes unrestricted support from Allergan, and from it's competitors in the pharmaceutical field.

[Slide.]

There was a lot of discussion this morning about the impact psoriasis can have on people. But I'd like this afternoon to emphasis a few important points about the disease.

First, of the more than five million Americans who have psoriasis, an estimated 1.5 million have a moderate to severe form of the disease.

The Foundation's national survey research has shown that for 75 percent of these people, the disease has a moderate to large impact on their daily lives. For 26 percent of these folks, it alters normal daily activities, and for 21 percent, it stops them completely.

For 36 percent, it causes trouble with sleep, and for another 40 percent, it affects how they choose their clothing.

For every one, moderate to severe psoriasis can profoundly affect one's work, family, and personal relationships.

[Slide.]

Here are a few photographs that illustrate how physically disabling and emotionally devastating psoriasis can be, particularly for people with moderate to severe cases.

[Slide.]

The Psoriasis Foundation believes there is a need for more treatment options for people with moderate to severe psoriasis. In addition to being a very serious disease, psoriasis is a chronic disease. It typically first strikes people between the ages of 15 and 35, but it can affect anyone at any age, including children.

Our research in 2001 showed that 78 percent people with moderate to severe psoriasis were not using aggressive therapies because of concerns about side affects and effectiveness. In a recent national survey, more than one-third of the patients said they were "very satisfied" with

the treatment they were receiving for psoriasis.

While there are several treatments available for moderate to severe psoriasis, none of these treatments work for everyone, or can be used by everyone, or necessarily works the same over time. An individual patient's psoriasis can change in severity, and even if type over years, months, or even weeks. Patients need and deserve choices that meet their individual concerns about safety, effectiveness, cost and access.

[Slide.]

The Psoriasis Foundation believes psoriasis patients should have access to oral tazarotene. It may offer many patients a reduction in psoriasis symptoms, and thus an improved quality of life. And its approval for the treatment of moderate to severe psoriasis would give an option to people who cannot use currently approved therapies.

The Foundation supports a risk-management program focused on women of childbearing potential to minimize, to the greatest extent feasible, the

likelihood that a women will become pregnant while taking this drug.

We hope Allergan and the Food and Drug Administration adopt a risk-management program that addresses this risk without imposing constraints that would effectively limit access to oral tazarotene for the many psoriasis patients whose lives might be greatly enhanced by it.

Finally, as with any new medication, the long-term side effects of oral tazarotene are unknown and need further study.

[Slide.]

In closing, moderate to severe psoriasis can dramatically and negatively affect a person's quality of life. People with psoriasis need and deserve more treatment options. And the Foundation believes access to the new treatment, oral tazarotene, is important and desirable.

By expanding the array of choices available to treat this serious chronic disease, we empower patients to choose the treatment that works best for them.

I know that the quality of life for my son and thousands upon thousands of people like him will improve dramatically as a result.

Thank you.

DR. STERN: Thank you very much.

Could speaker number two please come to the podium?

MS. FREEMAN: Before I introduce myself, I'd like to thank the National Psoriasis Foundation and the tens of thousands of people who support it for giving me the opportunity to tell my story here today and to represent the millions of people suffering from psoriasis.

I also need to say that I do not have a financial interest in the company that makes the drug we are talking about here today.

It is ironic that I should be here, as less than three weeks ago I was sitting in the clinical trial research center, and I had just filled out my monthly questionnaire. I closed the folder and went to date it, and next to the day was "Patient Number 1569." I looked at my new bottle

of pills, and again I was "Patient 1569," and I thought, "Gee, here I am, I'm really just a number."

So, today I want to introduce you to Patient Number 1569. My name is Janey Freeman, and I live in Yantis, Texas, which is two hours east of Dallas.

I'm married. I have two children, and I currently work as an office manager for a land developer and an insurance agent. And Yantis is as "country" as it sounds.

[Laughter.]

I was diagnosed with psoriasis when I was 20 years old. So for 34 years I have been injected with steroids, wrapped in tar, put under lights, and zapped with machines. I have used creams, lotions--not to mention slept wrapped in cellophane--and I have worn gloves and socks filled with all kinds of creams and lotions.

I have washed my hair with tar shampoo, and I've ruined a lot of towels and a lot of white bathtubs, soaking in all kinds of products.

I have also taken methotrexate. This made me sick two days out of the week. And about the time I was feeling better, it was time for me to take another dose.

I have had my blood drawn every six weeks for 10 years. And I have had one liver biopsy.

Psoriasis is not usually life-threatening, but some of the current treatments are. So, forced to choose between a quality and a quantity, I chose the quality.

What would my life be like had I not had psoriasis? I'll give you some examples.

When I was younger, I thought about modeling, but models don't normally have psoriasis. And then I wanted to be a dentist, but at that time my hands and my nails were really badly affected. So I chose a field where I could sit at a desk and be out of the public view.

I have missed a total of two years of work due to the disease. I have turned down two promotions. I missed my senior high school trip to New Mexico because I was afraid I might flare.

I have never had a manicure or a pedicure, and my best friend still cuts my hair.

From my early 30s to my mid-40s, I was single. My psoriasis was then at its worst, and I was too embarrassed to have an intimate relationship.

My closet has always had two sets of clothes: the clothes that I wear when my psoriasis is bad, and then my "sometimes" or fun clothes that I get to wear when my skin is okay.

I have had co-workers more out of my part of the office. I have had nurses put on rubber glovers for just a routine exam. And people have even moved to another cashier after seeing my arms or my elbows when I'm flared.

Psoriasis hurts. The lesions bleed. You itch uncontrollably. It's embarrassing, it's expensive, it's physically disfiguring, and mentally exhausting.

I can't really tell you what my life would have been like without psoriasis, but I can tell you that Patient Number 1569 is better because of

oral tazarotene.

The medicine I am using is not perfect, but I feel hopeful for the first time. My plaques are clearing, and I'm at least 60 percent improvement according to the research center, and I have no new ones.

My scalp is clear and the itching is gone. I've never been sick to my stomach, and the only side effects I have experienced are mild joint pain and the dry skin.

The first time I walked into my current dermatologist's office was 10 years ago, and I was crying. A few weeks ago, after my last exam, we both were smiling, excited and hopeful.

I believe that his drug--oral tazarotene--should be available to patients that it might help. With continued research and dedicated and caring physicians and staff, we can give hope and options to those millions of people like me who suffer every day of their life with psoriasis.

I thank you very much.

DR. STERN: Thank you.

And could we please have speaker number three come to the podium?

MR. GORRE: Good afternoon. My name is Tyrone Gorre. And I was born in Sacramento, California, raised in Newcastle, which is about 45 minutes northeast, in the Sierra foothills--and that's considered what is called "Gold Country."

I am a single, 45-year old fishing guide and ranch hand, who is currently raising two daughters--young adult daughters--who are seemingly unaffected yet.

I want to say thanks to the National Psoriasis Foundation for making this--giving me this opportunity to speak to you guys today, and I would like to say at this time that I have no financial obligation or commitments or interests in the company that makes this particular drug.

I've had psoriasis most of my life. I've tried many different treatments over the years, including UVA, B, psoralen with PUVA, most topical steroids, Dovinex, and Tegison and methotrexate. Through that period I really began to understand

what medical "practitioner" meant. That changed for me.

My psoriasis really started getting bad when I was about 25 years old. I had had it for a long time before that, but it really became more prevalent and widespread, with noticeable plaquing on my face and all over my body. At this time I was just a newlywed and beginning to have children.

Psoriasis had changed my life. I used to be a life guard and wear shorts all the time. I gradually changed my style of dress to basically go into a coverup. I would always wear long pants and long-sleeved shirts and even hats; collars, turtlenecks--anything to hide this terrible disease.

I was really embarrassed, because at that point I had psoriasis on about 40 percent of my body.

My daughter has recently told me that her mother said one of the reasons that she divorced me was because when I was young and married her I did not have psoriasis, and while we were married I got

psoriasis and it became very bad.

She said that his was a big factor in my divorce, and I really do believe it. It would be terrible to go to sleep at night, and have the woman I loved wake up covered in scabs and pieces of skin on her.

There was few years when I simply played cover-up, and hide my disease, because I had no access to health-care coverage, or no insurances of any form. So, I tended to worsen at that time.

Since I've had psoriasis pretty bad for quite a long time, I had known a dermatologist who was helping in research studies. At that time he had asked me if I would participate in a study of a new oral drug, tazarotene.

I thought about it seriously. At the time, I had had a nephew who was beginning to show signs of psoriasis. He was about the same age as I was when I got psoriasis, or noticed psoriasis. This was the extra motivation that I needed to join the study. I was willing to do this because I wanted to answer the question for myself, for my

family and all the people who I recognized as having this disease.

During the first part of my study I was 99 percent sure that I was given a placebo. There seemed to be zero effect. During the second part of the study, I believe I received the drug. The side effects that I noticed while taking the drug were basically my feet peeled one time, and I seemed to show some signs of achiness.

After about six weeks, I noticed the thickness of my plaquing beginning to shrink dramatically. And, man, my attitude was really changing at that time. I was really excited.

Within about four months, I was 95 percent clear. I had just small areas, and they were all less than the size of a quarter. My research clinic that I went to told me that I went from having 25 percent to 4 percent. That was pretty good improvement but, man, it felt like it was way more than that. It was much more of an improvement--in my mind.

At the point the study ended, I had only a

few patches of red skin that were very small. For the first time in my life, I was virtually clear of psoriasis.

Now, I wear flip-flops, open-toed shoes and shorts. I even wear black shirts now. For the first time in 20 years, I wore a black tuxedo with a silk collar. That's absolutely amazing.

For the first time, I would go to northern California and not get kicked out of the hot springs. For the first time in my life, I went to my health club and people didn't stare at me when I went to the shower.

I used to feel bad about this. The amount of mental pressure that is released is huge.

The confidence of not having psoriasis is amazing. It brings amazing confidence back. It was so rewarding to not to have to worry so much about this problem.

There are three huge things that this study has changed for me. One, with psoriasis you cannot sleep at night. The constant itching just absolutely drives you--and if you have a partner

would drive them--absolutely crazy, and it keeps them up at night also.

Two, you are so self-conscious about psoriasis that the psoriasis virtually eats your confidence down to nothing. You do not even want to be seen. So that's all changed now, too.

Three, the constant pain and stinging of psoriasis is incredible. This consumes a major part of your life. And now that has all gone.

Imagine this: take a mosquito bite--take the mosquito bite and get it on your knuckle. Take that itch that you feel, and multiply it times 20. Then scratch that itch for five minutes, until you break the skin and you make it bleed. And about the time you start feeling that that itching is gone, throw some salt on that wound and experience the burning of psoriasis. That is what I would feel up to a hundred times a day. And I've experienced that for over 20 years.

With that sort of feeling a hundred times a day, what kind of distractions from my life has occurred, and what have I missed in my life?

I will live with psoriasis for the rest of my life. I'm really glad that I got involved with this study, because it gave me hope, and it should give hope to other people with psoriasis, too. After more than 20 years of struggling with psoriasis, I feel like a new man after being on this drug for the short term that I was.

This medication not only improved my physical health, but it gave me back my self-confidence.

One thing that I hope this committee will do is make this drug available to patients who need it. I'm just a common laborer--a working man. And in most of the work that I do, I need tools to accomplish the jobs that I'm asked to do. And I really believe that there are not enough tools out there--and I've used the tools to try to take care of my psoriasis.

So I really hope that you guys have a strong consideration for people who are suffering like me.

This drug is definitely the least

threatening of all oral medications that I have taken. It has worked for me, and I've done this study for myself, for my family and for the thousands of people just like me all over the world.

Thank you very much for your time.

DR. STERN: Thank you.

Is there anyone who did not register who would like to come and present at this, the open public forum?

[No response.]

With no one so indicating, then we'll call this the end of the open public forum and more on to discussion and questions.

And, again, I'd like to thank the three people who presented for taking the time and traveling here to give us their feelings and opinions.

Discussion and Questions

DR. STERN: Until two o'clock, I would propose that we have the first part be questions of clarification--essentially what we did after the

sponsor's presentation in the morning, but now the questions could go to anyone: FDA, sponsors or, in fact, any other committee member.

So, if anyone has questions in terms of content, as opposed to really deliberation of the questions that have been posed to the committee--why don't we start with you, Dr. Honein?

DR. HONEIN: Yes, I just had a question of clarification from FDA.

My recollection at the February meeting is that we had recommended that pharmacists register rather than the pharmacy. And what I saw presented was the pharmacy in what was proposed for this.

So I was just wondering if I recalled that wrong, or what our final recommendation was?

DR. BULL: I would say, given that the overall program is not completely worked out, there are still a lot of details remaining. And I think some of the--is it on?

We're trying to look at what will be the most efficient way to ensure the risk management, and I think it may be premature to say exactly

which part. I think there was a lot of discussion at the meeting--as you recollected--on the issue of pharmacies and pharmacists. But I think that's an element of detail that is still being evaluated as what will be the most effective way to ensure that the elements adequately address the risk.

DR. STERN: I had a question for FDA; a little bit of a follow-up.

I know it's a very complex process, with multiple drugs and multiple sponsors. But are there other technical or external constraints that might be considered in slowing--potentially slowing the progress made toward developing a PLAS system?

DR. KWEDER: I'm Sandra Kweder. I was very involved in your meeting in February. I'm the Deputy Director of the Office of New Drugs.

And I had suggested to the group that I follow-up on this question, simply because it's an issue that's not only relevant at the working level in the division, but something that the agency and our office of chief counsel is concerned with, as well.

Probably the main--the sponsors have been working extremely well together, and this is really unprecedented among a number of generic firms and the innovator firm for isotretinoin. And I think it's fair to say that.

But, without going into a lot of detail, the patent issue appears to be potentially quite large. There is a patent held by--there are actually four patents held by Selgene Corporation on risk management--the concept, basically, of any risk-management program that links through one or more computerized data bases--patients, pharmacists who intend to distribute drugs, and physicians who may be required to provide data to that system. And the patents cover products where fetal toxicity is of concern, as well as any potential adverse event or contraindication.

So, these patents are available--you can find them at the U.S. Patent Office website. But this is the first time that we have encountered a situation like this, and it--our lawyers are studying this. But it does appear that it may pose

some obstacles to the implementation of a modified program as you recommended, and as we have been pursuing.

DR. STERN: Thank you.

Eileen?

DR. RINGEL: This may be a question for Allergan--whoever wants to answer it is fine.

I was wondering if patients who had erythrodermic or pustular psoriasis, that subgroup was identified and, if so, what the data about efficacy was for this medication?

DR. WALKER: I'll answer that for you.

We required the patients to have stable plaque psoriasis, and did not do a subgroup--or did not have patients actually enroll in the trial that had erythrodermic or pustular psoriasis.

DR. STERN: Dr. Day?

DR. DAY: I just had a brief comment about pharmacies versus pharmacists.

In the briefing document from the sponsor, it does say "a representative;" "a pharmacy representative." It does sound like one person

from each pharmacy--in the briefing document.

DR. WALKER: yes--I can comment on that.

We are proposing that a pharmacy be registered, and that there is a representative from each pharmacy who is responsible for training all the pharmacists within that system--really, to avoid problems such that if one pharmacist is registered, they all aren't, one gets sick, is out, that the drug couldn't be distributed. So the entire staff would be registered by one key, identifiable individual within that pharmacy.

DR. STERN: Dr. Katz.

DR. KATZ: A question for Dr. Walker.

Can the committee be privy to the expert opinions of people with expertise in bone metabolism?

DR. WALKER: They certainly can.

DR. KATZ: Can we--

DR. WALKER: Yes--

DR. KATZ: Thank you.

DR. WALKER: I have three different people here that have analyzed the data, and a fourth

person who, unfortunately, can't be here. But we do have the conclusions from that person. They've had a family emergency.

We have someone who's an expert on both the technology and interpretation of bone mineral density data; on orthopedic changes--calcification, osteophyte formation; and then an expert outside statistician who's helped us look at the data to see how these regressions from the mean, and are they what you would expect in this population as normal variance.

So it might be helpful for me if you tell me--if you want me to bring them up individually, or if you have questions that I can then field to the appropriate person?

DR. KATZ: The main question is what they would visualize as progression with the data that we've seen, combining the hip demineralization, the alkaline phosphatase--how that can be tied up. And what one would expect for the future.

DR. WALKER: All right--this is such a complex area. I have a lot of data in different

things. I'm going to start by having the statistician, who's looked at the data that we have, looked at the data from the 12-week study, and then looked at the data from the open-label 050P study, and has done some statistical analysis.

Now, he's looking to see: is there a variation that you would expect in the population?

So I think we'll start there. And then I'd also like to show you data that Frederick Bettingfield from Allergan will show you on: is this actually regression to the mean?

And we'll go from there. I think this could be fun.

DR. HELMS: Yes, I'm Ron Helms. I'm Professor Emeritus of Biostatistics, University of North Carlina, Chapel Hill. And I've been doing this a long time--someone suggested I say.

Probably a statistician is the last person you want to hear from, instead of the first. But there is an important point here.

Can we have the slide up, please?

[Slide.]

This is data from femoral neck bone mineral density evaluations. And I apologize from the lightness of the slide.

This is in the 52-week study. The red x's there are a scatter diagram. Along the bottom we have baseline measurements, and on the vertical axis we have the post-treatment or endo-treatment measurements.

And the primary point I want to make with this slide is that these data follow a bivariate normal distribution very closely. The data are closely approximated by a bivariate normal distribution.

Now, that would be more meaningful to the statisticians in the room than to others, perhaps. The consequence of that is that: if we see a shift from baseline to post-treatment over a period of a year, and if this bivariate normal distribution fits, then the shift shows up in the mean. It doesn't show up in other kinds of features of the distribution.

If you look on the bottom right-hand side

there, the man shift here was about minus .01; the mean shifted in 102 patients, I believe it was, from .943 to .933. And a similar median shift.

So, over a period of a year there was about a 1 percent shift in the mean; a decrease in bone mineral density.

While the slide is up I'll go ahead and make another point. I hope this is okay.

There has been some discussion about values that had decreased by more than 5 percent. There's a line that's very difficult to see, right along there--it's a green line--that's a 95 percent line, and that is--points below that line are points that were less than 95 percent at the end of treatment--less than 95 percent of what they were at the baseline. And there are some points in there.

The fact that this is a bivariate normal distribution actually means that that's not a very good way at looking at these data. The ellipse that you see there is called a 95-percent tolerance region, and it's designed to capture 95 percent of

the data points. And in this case, it actually captures 94 percent of them, which is a pretty good fit.

But looking at points that are below the line, where there was a reduction of 5 percent or more, there were 11 percent of those points in the data. If we were finding something going on other than just normal trends, just noise, that appears in these data points, we would expect to see more than 11 percent. Actually, we would expect to see 13 percent, just on the basis of noise. We only saw 11 percent.

So this is an indication--the conclusion from that is that what we're seeing here is just bivariate normal random variability.

Yes, sir?

DR. STERN: I wanted to ask you a question, because to me, it's very different when you're looking at sometimes rare idiosyncratic effects. So I guess what I'd like to know is: what was the power of this study to detect a 1 percent--1 percent of people having, in fact, 5 percent

reductions, and prove it statistically?

So, you've shown us everything fits in, but I don't know the power of this and how you've treated people without multiple observations.

So I would ask you--I'm interested in your assuring me, with 80 percent confidence, that not more than one in a hundred individuals has more than a 5 percent reduction over a year. What's your power to exclude that with a beta .8 and an alpha of .05?

That's, to me what's relevant in a safety study.

DR. LUE: I'm John LUE, biostatistics.

I've done some power calculation based on a 1 percent background information, what it would take to detect a 2 percent difference.

The power is about 11 percent.

DR. STERN: I'm sorry, is that a 2 percent difference in mean? Or one in a hundred individuals--

DR. LUE: One in a hundred.

DR. STERN: Okay.

So, in other words, there's an 89 percent chance that a difference--one in a hundred people could have more than a 2 percent reduction, and we wouldn't have detected it in your study.

DR. LUE: I need to qualify that. This was based on a sample side of average of 350 per treatment group. So a basis--

DR. STERN: This is only about a 150 people.

Dr. LUE: Correct.

DR. STERN: So the power of this is probably--

DR. LUE: Less.

DR. STERN: Less--like .05, .03--

DR. LUE: Right.

DR. STERN: --something in that--it's probably not linear.

DR. LUE: Correct.

DR. STERN: Okay. Thank you.

DR. HELMS: Let me just clarify one point, though.

There is a lot of--the substantial amount of power here for--and this goes back to the point I made about it being a bivariate normal distribution. If it really is a bivariate normal--and it fits very well--then the shift will show up in the mean. Even if there is a small subgroup, if it's a bivariate normal, the shift will show up in the mean.

DR. STERN: It all depends on how small a subgroup you'd be concerned about.

DR. HELMS: That's correct.

DR. STERN: And that's why I asked the question. One in a hundred, to me, would be a small number of people relative to those treated, but a clinically very important endpoint, were it true. And that's why I wanted to know the power.

So what I'm hearing is: there's not much power at all, here.

DR. HELMS: That's correct. I mean, there are 102 patients in the data.

DR. STERN: Thank you.

DR. WALKER: A couple more speakers for you

on the same topic.

DR. STERN: I'm wondering, if there's no power to reject the null, whether we should spend a lot of time. Because I have already an increasing list of speakers.

So, why don't we go on--

DR. WALKER: Well, umm--

DR. STERN: --to the next thing?

DR. WALKER: I actually think, if you look at this--and there's a lot of data in this field that I do think is important to look at.

If you look at osteoporosis studies, for instance, it's very common for patients to have a reduction as great or greater than what we saw on drugs.

So I do think it does lend credibility to what we've seen, and makes it a little more questionable.

We aren't saying that we don't know for certain that you don't detect a signal. We just think that the risk is minimal--not certain.

DR. STERN: I don't mean to be in any way

critical of the sponsor. I think we have to look at what we're looking for. And to my mind, what we're looking for--and perhaps other members of the committee would disagree--is a relatively low frequency event that could be idiosyncratic, and then we have to regard what is the quantity and quality of the data we have?

And I think I agree with you that we can't--these data do not either tell us that this drug is not bad for bones, or bad for bones, and that we have to live with that uncertainty. And I think we can look at these data five ways from Sunday--one of the things I'm a little too prone to do--and come to opposite conclusions.

But I think in the interest of time, we should probably move on.

DR. WALKER: All right. I actually appreciate what you're saying, and I think--I agree with you. I think my colleagues would agree with you.

The only thing to think about, when you think about the drug, is that it is a class of

drugs that we do have 20 years' experience with. And what we're seeing is nothing outside of what we would expect with the class.

Thank you.

DR. STERN: Ms. Shapiro?

MS. SHAPIRO: This is really a quite different topic. Okay.

I'm just wondering, from both industry and the FDA, if you can help me understand the purpose of, and impact of, the pregnancy test which, as I understand it, would be a part of this proposed risk-management program, as well--other than the first one.

In other words, when you do them monthly and you get a positive, is the purpose--are you going to then give counseling to that person? Is it going to be paid for by industry? Are you just doing it so you can collect data?

What--it's going to be too late, maybe, to prevent harm. So what's the purpose of it?

DR. WALKER: Do you want industry to start, or FDA?

DR. STERN: Did you want to comment on that, Dr.--

VOICE: [Off mike.] [Inaudible.]

DR. STERN: For some of us who've been part of this process for the last 16 or 18 or 20 years, it's been a subject of debate. And we could probably be here for about another week and not all agree on what it is.

It's--everything have evolved in a way, and there are varying opinions about which elements are most and least effective. And I think this is not the main purpose of our meeting today. And I'm--

MS. SHAPIRO: But, you know, with all due respect, if we're going to give advice on a risk-management program, I'd like to hear some of the proposed answers--in a nutshell.

DR. TRONTELL: Ahh--I can try and take the first pass at this--Anne Trontell.

You know, the purpose of ongoing pregnancy testing is, obviously, you would want to detect a pregnancy early and inform the patient about the

exposure and options available to that person. Education may have a secondary role, in terms of reinforcing the importance of adhering to contraceptive behavior.

And I would like--as a pointy-headed epidemiologist, and someone heavily invested in evaluating whether or not these various programs have an impact--it also gives us very important information to know whether or not the interventions that are being addressed, in fact are having their desired impact.

So, I think those three are probably what we think is most important about it.

DR. WALKER: I'd like to add that, actually, what's different in the program being propose now, and what's different in the recommendations for the new isotretinoin programs, are that there is a response to that pregnancy test.

You have a direct link--the pregnancy test has to be negative before the drug can be dispensed. Also, the educational materials--as you

heard this morning in the FDA presentation--the educational materials, there is a performance that the physician and the patient have to achieve that will trigger dispensing of the drug. If the patient doesn't understand the contraceptive measures required, and that they need negative pregnancy tests, then the drug, again, won't be dispensed.

So it is different than the current SMART program, in that there is--it's not just a pregnancy test. There is actually a response to that test.

MS. SHAPIRO: But if it's positive--it could have been positive for 29 days.

DR. WALKER: Well, the entry into the program requires at least two consecutive ones. But then, next, if a woman of childbearing potential gets it during her menstrual cycle then, in theory, you should be within a two week period. And, you're correct, it would just be stopping the drug very early, rather than, certainly, preventing the pregnancy.

DR. STERN: But, at least, for isotretinoin, the available evidence is that there is no safe period of exposure. There's a literature going back to the late '80s or early '90s based on the originator company's data that showed that.

So, early stopping, once a pregnancy has occurred in an exposed individual is--

DR. WALKER: Agreed.

DR. STERN: --a very serious event.

DR. WALKER: Agreed.

DR. STERN: Dr. Epps?

DR. EPPS: Sorry to return to the bone topic just for a second.

There were--I guess the company didn't comment on the fractures. I would like to know the type of fractures, and characteristics of those people.

DR. WALKER: Yes, we can show you those fractures. And we did go through the case report forms, and then go to the source documents at each site, for each fracture.

And Dr. Beddingfield's going to share that with you.

DR. BEDDINGFIELD: I'm Dr. Frederick Beddingfield. I'm the medical director of skin care at Allergan.

Slide up, please.

[Slide.]

We did go back and look at the fractures that were noted. We looked at several possible variables that could be associated with patients who had the largest decreases in the study.

And, as you can see from this slide, actually there were more than six fractures in the study. But what's interesting to note is that the age of the patient is typically young; typically male; and the sites of the fractures were mostly digits--and this has not been associated with decreases in bone mineral density.

If I could now have slide S-87, please?

[Slide.]

We looked at what were the bone mineral density changes in these patients, nonetheless.

Slide up.

[Slide.]

And what we found is that the bone mineral density changes within changes, and across the group, there's no consistent pattern, and there's certainly--one can see there's as many increases as decreases in bone mineral density. There's no clear relationship at all to these patients. And these were the six fractures mentioned, for which there was bone mineral density data. There's no clear relationship to the fractures and mineral density changes.

If I could just take a second and have slide S-183, please. There was mention in the briefing package of a patient with a 50 percent change in bone mineral density.

And--slide S-183, please?

[Slide.]

And just to--or, actually, slide S-183. Thank you.

[Slide.]

Just to set the record straight, this is

the recording we're talking about. And this is another recording from the femoral neck at the same time. And these scans were of unacceptable quality. I have further information on why they were unacceptable if you need that. But those were inaccurate results, and they were not accepted.

The patient did have some changes in bone mineral density, but they were much, much smaller, and nowhere near the same degree.

And if I could have slide S-206--there was one other patient who was mentioned, with bone mineral density change close to 30 percent.

Slide up, please.

[Pause.]

[Slide.]

Yes. And this is the changes in this patient over time.

This is the value that we're referring to. It's important to note that this patient was an over 300-pound gentleman, which makes this a very technically limiting study to perform. And most of the values were nowhere near this range.

However, again, there were consistent decreases in bone mineral density in this single patient, but certainly not in the range of this, over time.

DR. EPPS: Well, while you're handy, there was a comment, I guess, at one time that, you know, perhaps the gains or losses--depending upon which we're looking at--were per natural progression.

Do you have normal progression?

DR. BEDDINGFIELD: Yes, we have normalized the data.

DR. EPPS: Not normalized. I mean in the normal population--not on drug.

DR. BEDDINGFIELD: Okay, what we did--and I'd like to have our bone densitometrist speak to this--but what we did was to use a t-score evaluation, which is what the World Health Organization recommends. And it normalizes the data to the ideal adult male--young male bone mineral density. And it helps put it into perspective, because just because someone has a 5 percent change in bone mineral density doesn't tell

you where they end up. But the t-score does. It lets you know if they're osteoporotic, osteopenic, or normal.

DR. EPPS: Why weren't females used?

DR. BEDDINGFIELD: Well, that's something to ask the World Health Organization, I suppose. I wouldn't know the answer to that.

[Laughter.]

But that's a very good question [laughs].

Could I have slide S-196, please.

[Pause.]

Slide up, please?

[Slide.]

And this is a summary of the t-score results--in the patients with 5 percent losses.

What we found is that these would be--the patients with the worse losses in the study, that we're specifically looking at here--44 percent of them had normal bone mineral density throughout the study, all measurements; 38 percent had osteopenia at baseline, and they never became osteoporotic.

Just to put this in perspective,

osteopenia is 1 standard deviation from the mean; osteoporotic is 2.5 standard deviations.

16 percent who were normal did develop osteopenia. No patient in this group--not a single one--developed osteoporosis. There was one patient who started osteoporotic, and remained osteoporotic.

Notwithstanding Dr. Stern's comments about the power, which I certainly appreciate, I think this is at least helpful information on the patients with the most significant losses.

DR. STERN: I can't resist once more saying that: these are one-year data for a chronic disease, which we've heard earlier, has an average duration in severely affected individuals of 40 to 60 years.

So, what we're looking for is some little signal. If we had one patient who went from normal bone density to osteoporosis in a year without some other explanation, we would be--we probably wouldn't be meeting here today.

So, we have to look for subtle signals.

And I don't find these one-year data--this distribution--terribly reassuring.

[Pause.]

I'm sorry--Dr. Wilkerson.

DR. WILKERSON: I agree. I mean, we're talking long-term disease here. We have a signal from laboratory--just anecdotally, from years of retinoid use, I've rarely seen elevated alkaline phosphatase with the other products on the market.

So, obviously, there's something going on with this drug. The sponsor didn't pursue any more clarification of that. And, you know, as much as we want to dance around this data here, we've got another signal from hard-core laboratory, that is reproducible, indicating a problem, you know, with metabolism.

Now, is this drug going to be labeled an and on-and-off type drug? Or is it going to be labeled as a continuous administration? I mean, what are you going for?

DR. WALKER: Our proposal is to have the drug for chronic use. We studied it up to one

year.

We feel that the bone changes are minimal and rare. I do fully agree that a rare event cannot be picked up in clinical trials. This isn't unique to this product, it's any product at the time of approval, if it is a one in 100,000, or one in 10,000 rate of occurrence, you will not pick it up in most clinical development programs.

DR. WILKERSON: But, in all due respect, we may be talking about one in a hundred, or one in 200.

DR. WALKER: But you won't--

DR. WILKERSON: Not that rare, rare event.

DR. WALKER: Okay. I agree.

DR. WILKERSON: The n of your study is so small--particularly for the long-term administration of this product. I mean, you've got far too few people in your studies right now. That's the problem.

And while we need some alternatives--and I think that's what we're all here for, is to offer patients alternatives, we also, as a clinician, we

need to offer them things that we are relatively sure are safe for them to take long term--in five years we don't discover that, my God, you've got 30 or 40 percent bone loss, you know, sitting here, and you're 35 years old, and now you're osteoporotic at age 40.

DR. WALKER: I absolutely agree with everything you've said. But this drug is a new drug, and this is a new indication for an oral formulation. This is not a new class of drugs.

DR. WILKERSON: No, you're right. But we have not--either we have missed the boat with the other products on the market, and we have not detected this, or, because the selectivity of this particular drug, we are seeing a new side effect.

DR. WALKER: I--

DR. WILKERSON: This is not something that has been worried about with other retinoids that have been on the market. We knew about the DISH syndrome. We knew about calcification on the ligaments. But bone mineral loss has not at least been on the radar screen of clinicians for use of

retinoids in the United States.

DR. WALKER: Well, there are published reports of bone--

DR. WILKERSON: There may be--

DR. WALKER: --of bone mineral loss with isotretinoin. If you look at the labeling for isotretinoin and for acitretin, there is an alkaline phosphatase that increases up to 30 percent.

So, I do--you know, agree with what you're saying, but I take a little issue that these are new or unique events with tazarotene that haven't been observed in the class.

I do agree that it is, in general, not a major concern to clinicians when they start patients on acitretin or isotretinoin. However, when I trained, I did check x-rays in patients on acitretin for beyond--or, at that time, it was etretinate--beyond one year. And we did follow them routinely.

So, I do think that for chronic use, some physicians feel differently. I might help if I had

one of our experts--Dr. Lebwohl, who's used a lot of retinoids--comment on how he sees this drug relative to others

DR. STERN: I think we're going to just run out of time.

DR. WILKERSON: But, on the other--not to beat this bag of bones and move on--the other issue is: is this risk-management program that's being proposed going to be restricted also by these patent restrictions that we're talking about? Or is your program exempt from that.

DR. WALKER: Well, I have not been involved with the discussions for isotretinoin to be familiar enough to comment on whether we will be.

However, if we are proposing and adopting all the essential elements of isotretinoin, which is what I've been telling you, it's very likely that we may have the same restrictions.

But I would have to defer that question, actually, to the agency for comment. We haven't been involved in those discussions.

DR. WILKERSON: Could I hear from Dr.

Lebwohl.

DR. WALKER: Yes. Thank you.

DR. LEBWOHL: Sure. Mark Lebwohl--dermatologist in New York.

First, I would say that the amount of data regarding bone density that is presented here I think compares very favorably to what has been presented with the other retinoids that are available on the market.

Now, we do have a long history of use and, in fact, large numbers of patients who have been on oral either etretinate or acitretin for many years. And certainly in those patients I don't doubt that there is an amount of mineral bone density loss that can be found if you look closely, but it is not clinical significant. We're not seeing fractures--we're not seeing the kind of changes that you see with systemic steroids.

So, while--you know, I think that the kind of statement that is in the package insert for those drugs is appropriate for those drugs, I think it does put into perspective what we're seeing in

clinical practice both with this drug for, albeit a shorter period of time, as well as with those drugs over a long period of time, it's not clinical significant.

And I'm not aware of any clinician nowadays who routinely gets mineral bone densities or x-rays in patients on oral retinoids for years.

You know, the person who actually knows this better than I is Tom Fuerst, because he was telling me about this with other drugs that are actually used to treat osteoporosis.

DR. FUERST: My name is Tom Fuerst. I'm trained as a medical physicist. I've worked in the area of bone densitometry for the last 10 years, using it to assess osteoporosis and fracture risk, and monitor changes in bone mineral density, And I just wanted to make a comment about the potential long-term effects.

I don't have the answer to that. I don't think the data in this room to answer that question. But, in general, it's difficult to extrapolate from shot-term data to longer term use.

The general trend, whether you're introducing an agent that will increase bone mineral density to treat low bone mass, or another agent that might have a deleterious effect on bone mineral density, in general the changes are larger in the first six to 12 months, and not sustained afterward. There may continue to be losses, but just a simple linear extrapolation is difficult to do.

But, again, I don't have the data bout long-term treatment with this drug, but just a caution about extrapolation.

DR. STERN: Dr. Sellers?

DR. SELLERS. This is actually a very basic question, and it has to do with efficacy.

When I read the literature on efficacy, I don't see a significant difference between the oral formulation and the topical formulation. And I was wondering if you could comment on that?

DR. WALKER: I can. I was--first, I guess, you want to phrase things that it's very difficult to compare study to study. This assessment is the same, but the population was very different.

The patients who came into the topical trial did not need to be as severe as those that came into the oral trial. Their average body surface area was--around 10?--7 to 8 percent body surface area. Their disease was less.

We also had, for our criteria for efficacy, not a "none" or "minimal," but actually a "mild," "none" or "minimal." And those trials, very few patients actually made it to none or minimal. And I'm not sure--in Dr. Cook's analysis, I think you might not have meant "none" or "minimal," but "mild." Because when you look at our label for "none" or "minimal" the numbers are actually smaller than what was presented today.

So I think it's difficult to compare. I think large body surface areas are difficult. The drug works, I should say, very well topically. But it's really a different patient population.

Also, the topical drug is not appropriate for intertrigenous areas because of erythema, scaling and pruritus. It's difficult to put a gel or a cream in the scalp. It doesn't help nails.

I will say although we didn't see nail changes in the 12-week study, we did see positive effects in the one-year study. You wouldn't expect to see nail changes in a 12-week study based upon the growth rate of nails.

So, there were other effects that you can get long-term that you wouldn't get with a topical.

DR. STERN: Dr. Epps?

DR. EPPS: I have a question--just to change organ systems--about the thyroid issue. Were any of the patients symptomatic? What was the outcome of some of those patients' alterations?

DR. WALKER: I'd like to share that data with you. I think it's a complicated area, and when you look at the data, it just shows you how much variation, also, you get with thyroid within a patient population.

And Dr. Beddingfield is going to share that with us.

[Pause.]

DR. BEDDINGFIELD: Could I have slide S-188, please? Slide up, please?

[Slide.]

This is the data that we have on thyroid disease, and thyroid labs from all three studies; the placebo-controlled trials, the six-month trial, and the one-year trial.

And this is adverse events. So this is hypothyroidism, as reported as an adverse even in the placebo-controlled trial. There's no difference between the tazarotene group and the placebo group.

We also looked at patients with percentages of TSH that were abnormal. And you can see there's no difference between the two groups.

Thyroxin level--no significant difference between the two groups--a trend for the placebo group to have a higher rate of abnormalities.

And the similar pattern is seen throughout the trial. You do have, here, a slightly higher rate in the long-term treatment with tazarotene, versus the 12-week treatment. This was not statistically analyzed, but you can see the rates of TSH abnormalities and thyroxin abnormalities

follow no consistent patterns there.

And then in the long-term study, comparing the first six months of treatment to the second six months, you don't see a spike up in the second six months. And overall, the rate of adverse events for hypothyroidism is quite low, and the comparable rates of abnormal TSHs and thyroxine.

So, I really do not think we've seen a signal here at all with respect to thyroid. And, of course, this is quite different than what we've seen with other retinoids.

DR. LEBWOHL: I just wanted to comment--the reason that we looked at hypothyroidism in these patients is because of a known retinoid effect in causing central hypothyroidism, which is different than what we're seeing here. With Targretin or bexarotine, you see a drop in TSH, which then leads to hypothyroidism, and the TSH remains low. So the elevation of TSH is not a retinoid effect that we're used to.

DR. STERN: Dr. Honein?

DR. HONEIN: Yes, I have a question about

any predictions that FDA olor the sponsor has about off-label use, since in the trends you presented for the topical version of this drug, three-quarters of it is for acne.

And what I heard presented this morning is sort of focused on the psoriasis population being different. But if three-quarters of this drug is going to be used for acne patients, I think that would need to play into what sort of risk management program is appropriate.

DR. WALKER: Topical use for acne has been proven to be effective. For oral use, we did do a Phase 2 dose-ranging study, and we showed some efficacy. Whether it's as efficacious and would meet the criteria for approval for nodulocystic acne is not known. We're currently not pursuing the Phase 3 program for the acne indication.

It's, I think, somewhat of a leap of faith to feel that 75 percent of the oral would be used for acne, since it hasn't been proved. It certainly--not all systemic retinoids work for acne. Isotretinoin is very unique. Acitretin,

etretinate--altrans retinoic acid--bexarotine--three other systemic retinoids, don't work for nodulocystic acne, and haven't been proven.

So, I think that the logic is there, but it's not--it is somewhat of a leap of faith.

Allergan won't promote this product for off-label use. We won't encourage off-label use. We won't do any of those things. We will promote the product to be used on-label, which we're requesting to be psoriasis.

Having said that, we do have a risk-management program that does target the vulnerable population, irrespective of the use of the product. So we are protecting the patients to, really, the same degree that the isotretinoin program is protecting them. So in the event that it is used off label, that population would be protected.

And the next question, of course, is how would you track where it was used, and we would track that through known marketing data bases, such

the IMS data base, or automated data claims bases.

DR. STERN: But, the FDA, in their briefing document, in fact, gave as illustrations a number of studies that were presented as posters, which showed various kinds of efficacy in acne for your product, and I know you would not promote it as such, but one--in fact, if one looks at the oral retinoid use, there's at least an order of magnitude difference in the number of people exposed to isotretinoin than all other oral retinoids combined, with acne versus all other indications.

And the problem, to me, is that who is to say that even without promotion, given that you have a product that is topically used both ways, that the average clinician won't think, "Oh, tazarotene--something new. Works well topically for both indications." And I guess my concern is: in any off-label use, unless we have evidence--you know, this is not the usual off-label use, but rather, we have a drug with known substantial risks, and then we have a drug with what might be

the dominant use--at least if it conformed to the overall use pattern of retinoids--being in acne. And I don't know what the benefits are in acne. You know, if you could present me with data that showed the benefits are equal to isotretinoin, and you only use it for 20 weeks, and the remissions are the same, I'd feel pretty good about--very good about it, in terms of approving it now, and then letting your NDA go forward.

But let's say this is a drug that doesn't give remissions, and people use it in a different way for acne, with more exposures. You know, it's not the usual--"Well, they might not have gotten approval." This is a class of drugs we're extremely concerned about. And the psychology for it, based on topical use, and based on some studies that the company must have sponsored and saw fit to have--let their individuals present at meetings, has an acne claim, basically. You know--psychologically.

And before you answer that question, I'd like to pose a related question to the committee,

and I'll start it by showing my own ignorance.

Is there anyone else who's a dermatologist on this committee that knew that the labeling for topical tazarotene asked for a pregnancy test within two weeks of starting? That's my first question. Was there anyone else besides me who didn't know about that?

Okay. I guess that means I don't have to ask the second question: how many of you routinely do it. [Laughs.]

DR. EPPS: And no representative has ever told me that they should.

DR. STERN: And it's a very well sampled product in the places where I practice. So it's not like we haven't seen the folks--which I think--so that really concerns me, too. You know--

DR. WALKER: Well, there's two very complicated questions--or really more ideas that that you've placed out there.

I'm going to start with the idea of the acne, and the oral tazarotene.

I think you have to keep focused on the

fact that oral tazarotene works very well for moderate to severe psoriasis. The acne issue is out there. It is a retinoid. You can make that leap of faith. But really, to restrict a drug for severe psoriasis patients because you're concerned about off-label use, I think is a bit inappropriate. And the drug does work for psoriasis, and that's why we're here today. I want to remind you. I want you to think about what the patients said that were here, and to keep focused on all the work that we've done in the psoriasis indication.

We have done some Phase 2 work for acne. We presented that Phase 2 work at meetings. It does suggest some efficacy. Whether it's close to Accutane; whether you don't have relapse like with Accutane, we haven't demonstrated.

You know, I don't think it's going to go off and be an Accutane in the first year. We would follow all that. If modifications needed to be made because there was vast, you know, off-label use, then I think that would be something that

could be discussed with this committee, with the agency. But, you know, I really almost want to be you: don't forget what we're really looking at. Don't forget those pictures of those patients.

You know, this is for psoriasis. It does work. We do have a very rigorous risk-management program in place--or that we are going to put in place, which is--it has all the components that he isotretinoin program has. So we are tracking those patients. We are protecting those patients, because--we appreciate your concern, but we don't think this should be restricted until we prove or disprove that it works for a separate indication.

The other question that's out there is the topical. It is clearly labeled. We do have all our advertisements that have it. And the reason you probably don't worry about it is that it isn't a real risk. It is a very, very low systemic absorption. We've had, I think, eight pregnancies. I could show you that data. There's been no retinoid-related effects.

If you look at the serum concentrations

with topical administration to the face for acne, relative to the teratogenic levels, they're very, very low. So, although it is a risk, the company supports the X label. We don't advertise against the X label. It's in all of our literature. That--you know, the company isn't saying this, but I think the fact that you're not that aware of it is because it's not a real significant risk.

We aren't saying that with the oral form. We're saying it is a significant risk. It is a probably teratogen. And we are willing to go beyond what any the retinoids out there are doing right now. We're going beyond what the competitive retinoid is for psoriasis, and we're going beyond what bexarotine is, which is for cutaneous t-cell lymphoma.

And just keep your focus--I'd like to say on psoriasis and on the patients who need this drug.

DR. STERN: Dr. Sellers.

DR. SELLERS: This issue is somewhat problematic, though, because, in fact, all you

really need are the data from a Phase 2 trial to establish your off-label market before a drug gets approved for something else. And, in posters that were cited were discussing efficacy, were discussing safety, that were based on trials that may not capture populations at risk for pregnancy exposures, for some of the adverse events that we discussed today.

So, I think although the company will not be--quote-unquote--"promoting" the use, it's already out there. And there's no way we'll be able to control it, unless we continue with trials.

DR. WALKER: I will say that we did do safety monitoring in that population, because the risk of pregnancy, I really think we are covering.

But if you think about bone mineral density, the x-rays--we did extensive studies in that population. We looked at epiphyseal plate closure, we looked at bone density, we looked at osteophyte formation. We also did urinary markers for bone resorption and absorption, as well as fractionating--in that case, the alkaline

phosphatase. And we didn't see anything. That was a six-month treatment.

So, for short-term treatments like what you have with isotretinoin, you don't see the same adverse event profile that you may see out beyond a year.

DR. STERN: But you did see three out of either 84 or 86 women enrolled in your clinical trials become pregnant--with, presumably, since these trials were relatively recent--presumably a company risk-management strategy for the management of the Phase 3 trials.

So--you know, that's not a great number.

DR. WALKER: The trial--although it has essentially--it has a mandatory registration, since the patients are in the trial--there wasn't the extensive patient education. This was done several years ago. There wasn't the mandatory patient education. And then the reaction if the patient didn't demonstrate appropriate education, which is now being employed in the post-marketing of oral tazarotene

So it is somewhat different, although I agree, there were pregnancies and that concerned us, and that's partly why we've modified our program.

DR. STERN: Dr. Katz.

DR. KATZ: First I have a couple brief comments.

Dr. Epps asked the question: how does the decreased bone mineral density compare to what would normally be found? In the FDA presentation we were told less than 1 percent in males per year, and here all the trends are greater than that.

Another comment to Dr. Sellers, when she asked Dr. Walker whether the comparison with topical and oral was similar. I would like to emphasize, again: these were not double-blind studies. And for the non-dermatologists around the panel: topical, tazarotene, it gives irritation. So it's unblinded immediately.

Nevertheless, all the studies you see are entitled "double-blind" studies. You have to start as double-blind studies, but anybody knows that

they weren't double-blind studies.

The other thing I would take issue with--and there could be difference of opinion on this--Dr. Walker, I don't know if you actually treat patients--with the Tazorac, topically, but you repeatedly state "it's very effective in psoriasis." And that's all I do. I teach a half a day, and otherwise I take care of patients, many of whom have psoriasis. And it's not very effective topically. You know, it may be in the rare person. I haven't seen them in 10 years. But it may be. But it's certainly not very effective.

And soon after it came out they were suggesting its topical use with--I don't want to be argumentative now, but topical use with topical steroids. And it is very effective with the use of high potency topical steroids, which work by themselves.

Now, to get off from that, my own comments are that these bone--not only bone density that bothered me, but it's all in the same direction: elevation of alkaline phosphatase, more retinoid

musculoskeletal symptoms. And it's all in that direction. And it's only in a 52-week study. And you worry about these patients long term.

It's unlike Accutane, where we treat patients for 20 weeks or a little longer, and a small number require--well, not so small number require re-treatment, but it's for another 20 weeks. It's not with continued use.

So you really worry about an effect like that.

And we can't use the argument that we have 20 years of experience with it, because we don't. This is a different drug. It's a unique drug. It only produces cheilitis in 65 percent of patients, whereas Accutane, it's 100 percent of patients. And so its unique effect on bone is not astounding. And, in fact--in disagreeing with a colleague--in the rare instances where we use Accutane long term--which is rare, like in Darrier's disease--we do check bone density after a year. We are very concerned about that.

But this appears to have even more of

those effects.

DR. WALKER: I'd just like to comment.

Number one, I've learned about the double-blind from you, and I made a not during lunch. So thank you. I think you're absolutely correct. I've been accused before having that "very" in there, and I need to strike those from my vocabulary. So that's another friendly reminder.

And also I think your point about the bone--we understand what you're saying. I do feel that it is within the range of what is reported in the literature for the other products, but I understand what you're saying and we appreciate your opinions. Thank you.

DR. STERN: Dr. Day.

DR. DAY: The proposed brand name for the oral is "Tazoral?" Is that the way you say it?

DR. WALKER: "Taz-oral."

DR. DAY: Well, I've gone around and asked a bunch of people, and I've gotten lots of different pronunciations, even from dermatologists. So that could be a problem.

But there is a precedent with Tazorac out there. Have I said that correctly?

DR. WALKER: You have said that correctly.

DR. DAY: All right. When you write both of those--and if you happen to write in block letters, the "C" and the "L" at the end could look very similar.

The Drug Safety and Risk Management Advisory Committee has been concerned with confusion in drug names. And it is the same active ingredient and so forth, but since there are different indications for the oral and the topical--and also different effectivenesses for the different types of psoriasis and location for psoriasis, could you comment on the implications of a patient getting one, as opposed to the other, and vice versa?

DR. WALKER: Yes, I think you bring up a very important point. I think Tazorac is easy to say, partly because a lot of us are used to saying. The Tazoral--you know, I think that that has to go through market testing and to see if patients

understand it, if they can distinguish it, if--you know, there's specific testing to do for writing it.

And, to be honest with you, I don't know how much of that's been done. If Tazoral is not the perfect name, then I think we can always work on another name.

I feel it's important to have separate names for the separate products, for a lot of the reasons that have already been voiced here today. Tazorac means acne to people. I mean, everyone around the room says "Tazorac, acne--effective for acne."

If you have a separate name that is separated by the indication and by the severity of the disease, I think it may help--although it is the same active ingredient--I think a separate name can help distinguish a very separate safety and efficacy profile that this drug has.

DR. DAY: So, do I understand that the market testing on this is not completed, in terms of multiple pronunciations? I mean, I've gotten

"tayzer-ell," and all--

DR. WALKER: I will have to--I'm going to ask one of my colleagues, because I am not in the marketing group, I'm in the R&D group. So I'm going to ask--and I'll answer that in just a moment.

[Pause.]

It was initially tested. But because of the comments and feedback that we got actually just a couple of weeks ago, we are re-testing that to look at it, taking into account what you've said.

DR. STERN: Dr. Gardner? And I hope I pronounced your name correctly.

[Laughter.]

DR. GARDNER: Yes, you did, Dr. Sterm. Thank you.

[Laughter.]

You know, I'm becoming increasingly confused about what the risk-management program is. Because as much as I have to confess to resisting Dr. Walker's lecturing the committee about what we ought to be focused on, the fact remains that if

you were to put a comprehensive risk-management plan the way I think it's been described here, with anybody who prescribes the drug has to be registered; and anyone who gets it has to be registered; and anyone who dispenses it has to be registered--then it seems to me it almost doesn't matter whether it's being prescribed for psoriasis or acne. We would pick up on it if, in fact, the risk-management plan--you can't get it unless you go through this plan.

And even if that's true, then Dr. Day's most recent comment is very, very important. Because if someone is restricting Tazoral in this way, and protecting everyone from harm--or, theoretically, by it. Then if a prescription comes through for Tazorac, and is mis-filled, then all that protection goes out the window, because someone mis-read what was written on a prescription.

And so I guess I have two points: is the plan--the risk-management plan as we understand it--supposed to be comprehensive, regardless of

what the prescriber is thinking the indication is; and, two, how to protect against a mis-reading of a written prescription?

DR. WALKER: I want to thank you. I think you've said what I tried to say earlier more eloquently and efficiently.

Yes, the program--that's why we want a separate name, to keep it separate. The risk-management program would protect all vulnerable patients regardless of the indication. The indication could be tracked through marketing data bases. So you could track it. All those patients would be protected. And I think a name helps with confusion at the pharmacy. It actually helps the patients who need topical Tazorac don't have that restricted because they get confused with the program.

So what you've said is actually what the company agrees on.

DR. GARDNER: One more thing--if you're really registering everyone, then you shouldn't have to track it through IMS data bases, because

you ought to have total coverage, shouldn't you?

DR. WALKER: Mm-hmm. Well, that doesn't do indication, per se. Indication is not tracked as part of the proposed registry for isotretinoin or for the oral tazarotene formulation.

I have some other folks up here who'd like to make a comment.

DR. KRUEGER: I'm Jerry Krueger, University of Utah. Just on the Tazorac oral and the Tazorac topical--you can't have a prescription be complete if you just put down "Tazorac." The pharmacy will call you up and ask you, "Do you want the gel or the cream?" "Do you want .1 percent or .03 percent?"

So I don't quite see room for confusion.

DR. DAY: It can go both ways. It could be "Tazoral--"

Dr. KRUEGER: So,

DR. DAY: --to Tazorac and vice versa. And, furthermore, in electronic scrips, you might say, "Well, then you don't have to read handwriting." But there's a lot of scrolling down

and tapping, and you can mis-tap.

So this is a potential thing that is very likely to happen. And we just need to think about what the consequences would be, going in both directions.

DR. KRUEGER: Yes, I can see some real concern going in one direction. I don't see much concern going the other. Thank you.

DR. STERN: Dr. Levin.

DR. LEVIN: A couple of questions for the sponsor, and then back to the FDA, and where we are with risk-management programs, because I think that's key to how this afternoon proceeds.

Question to the sponsor: why aren't you--or would you pursue a Phase 3 trial about the use of this drug for acne, which would perhaps answer the questions about whether this drug is safety and efficacy for acne use, and might reassure people who are concerned about its off-label use. So that's a question. Don't you see this as an issue, and if it is an issue, are you willing to pursue it in the right way--in my

opinion--which is to go for an approved indication using the approval process.

DR. WALKER: It's been a very difficult process. We have met numerous times with the agency on this. And I'm looking now at Khalyani Bhatt, because she can verify we've asked her for numerous meetings on this.

It is a very difficult trial to do. We have had discussions--and maybe Dr. Wilkin wants to add to what I'm saying--what we've been asked to do is do a head-to-head comparison with isotretinoin for five to six months, and then follow the patients out for one year.

In order to have the power to do that, that becomes an incredibly large study, if you add x-rays and many things. It almost--and the parameters that we've gone back and forth that we need to do--becomes a study that is so onerous that the company is not sure--with a lot of risk knowing whether the drug works or not, based upon our Phase 2 data. You always take your data and you extrapolate as to whether or not you feel you can

win.

At this point, we don't feel ready to do a Phase 3. We don't feel that the Phase 3 designs that we have discussed back and forth with the agency--not saying what they've asked us to do is wrong, just saying what we can accomplish as a, you know, mid to small pharmaceutical company for a dermatologic indication, that we can actually do that.

So it's become a feasibility, economic, and a very difficult study to do; to put all the bells and whistles. I mean, you know, if you imagine everything that's been in these trials; you imagine every controversy that surrounds isotretinoin, and you try to put that in a study to look at comparability--which are much larger studies; you multiply that times two, and you take that out two years--because you're, at minimum, six months enrollment--six to nine months, enrollment; you've got another six-month trial; you've got a year beyond that, follow-up, to look for relapse. You need to win on relapse rate, not equivalence at

six months.

That just becomes a study that we're not sure we could ever do.

DR. LEVIN: Okay. Another question: you look at the Accutane risk-management program as sort of the ceiling, and I would suggest you might want to look at it as a floor. And let's go back to the indication issue.

For example, one of the things that perhaps could be built in here as a requirement for ICD code-9s to be submitted, and actually not filling a prescription where the coding--if ICD9 code's the appropriate code--isn't the appropriate indication. I mean, that's a new way--that's a new way of looking at risk management.

But, again, I don't think Accutane is necessarily the ceiling here in how we manage risk. It might be a floor or a mid-way point, and we could add to it.

So, it's just a question--

DR. WALKER: Yes.

DR. LEVIN: If this is an issue that people

are concerned about, rather than relying on marketing data, why not try to--and, again, I don't know if this is, you know, feasible or not, but to think about, talk about, building in a requirement that patients only get through the system if they have an appropriate indication that is entered into the system, as an ICD9 code or whatever.

DR. WALKER: It's certainly feasible. I think, for the practice of medicine in general, it's not desirable. And I don't know if any clinicians, either on the panel or in the room want to comment on it.

You know, in dermatology--and I can see, you know, that is--if it was determined to be such a risk, it's certainly something that could be applied. However, in dermatology, I know--I am, I was asked before--I do still practice, but I think in the opposite ratio of Dr. Katz in terms of time spent doing research versus seeing patients.

In dermatology, a lot of our drugs don't have approvals that are indicated. And I think that doctors use drugs for many uses. So we

wouldn't--you know, I can't talk out of both sides of my mouth--

DR. LEVIN: This isn't every drug. And one of the challenges we have when we discuss a drug which has some unusual risk profile is that we're always operating with a knowledge that there is diagnostic creep; and that a drug where we're weighing the benefit and risk of toxicities versus the benefit--and nobody is--you know, no one is against providing relief to people who are suffering some psoriasis that is refractory to other treatments. Nobody's saying that.

But we have this equation we have to go through.

Now, one part of the equation is very slippery, because it's called--you know, the diagnosis, or the indication for the drug. And we sit here knowing that it's going to get used for lots of other things besides that part of the scale that we're sort of judging against the risk part.

So--

DR. WALKER: I agree. I think that you've

proposed something that could be considered. I'd be interested in other people's opinions. It's hard to argue that it shouldn't be considered.

DR. STERN: Might I suggest that there's at least, in the PDR, one example of a drug where for certain in what was once the dominant use of the drug now has a black-box warning. If you look at Allopurinol, it says very explicitly, "This drug is not for the treatment of asymptomatic hyperuricemia," the reason being, in fact, an extraordinarily low-risk of Stevens-Johnson system and hypersensitivity syndrome in association with the drug.

And I guess that goes to my point: as opposed to what I've heard is, we're not sure enough that we can win the battle against Accutane with respect to efficacy--and efficacy, to me, means benefit in the acne indication. Maybe what we need to hear from the company--I don't like things that say, "Oh, let's restrict use." I'd like to hear more from the company about how we're going to educate physicians about, in fact, making

sure that they understand the proper use in areas where, because of the risks of the drug, it's not a good idea to use it, as opposed to a label and things.

I'm wondering how willing--and how we would then monitor, in fact, the follow-through of the company in terms of making sure people understand where we might be confident the benefit-risk ratio is an appropriate one.

DR. WALKER: We plan to do that through two ways--if you could bring this first slide up?

[Slide.]

Okay. We have designed a "What a prescriber needs to know" brochure. We also have a prescriber introduction letter; a prescriber certification test--and that test will be part of the same system of you prove that the prescriber understands, just like you prove the patient understands their risk, you have to prove that the prescriber understands the risks and limitations of the drug, as well as having a medication guide.

We also will have scientific meetings to

certify physicians to be into this registry. They can't be in the system, they can't prescribe the drug unless they've gone through the process.

So those physicians that go through the process, part of that process will be educating them that this is for psoriasis, what the labeled usage are, what the risks of the drug are, as well as the pregnancy risks. So all risks will be discussed.

Now, Dr. Andrews would like to kind of go through the flow chart of the risk minimization action plan.

DR. ANDREWS: Thank you--

DR. STERN: I think we better not do that now. That was not really responsive to my question.

It's not "what's the usual stuff?" I was sort of hoping to hear something new and different that might really work. You know, these kinds of things are things that the pre-1988 Accutane interventions. I happen to believe that the 1988 Accutane interventions were better than we heard

today, but that's strictly editorial.

So I was hoping to hear something imaginative, impactful, innovative and with, on might think, a reasonable chance of success. And I know--I could see Dr. Furberg having the same kind of reaction to this

DR. FURBERG: I agree with you. And I think that we need also some way of going after people who are not complying. There should be--a stick there, somewhere--not just pleading. Because if you ignore this, there's no consequence.

DR. WALKER: Well--

DR. FURBERG: We need to set up a system so that people do comply.

DR. WALKER: Well, I think I'm hearing two things: one--I mean, I've got some things up there: "What would be the roll out?" I don't think that answers your question. There's nothing really innovative up there.

I would love to hear--and we're very open to any kind of innovative feedback that this group wants to give us here, or in private.

But what you're saying about consequences--this system's a little different than what exists now, in that you register the physicians. There is a feedback as to whether they understand the system, and there's feedbacks that the patients comply. There's feedbacks at the pharmacy. And there's checks and stops all through the entire system.

I won't go through it in detail, because I think a lot of you already kind of know what that flow chart is. But it's different in that the consequences--if you don't admit that you understand, you don't follow the system, your patient won't get the drug. It will not be dispensed to you.

DR. STERN: Dr. Honein.

DR. HONEIN: Yes, I just wanted to add a suggestion to what Dr. Levin said: that we could add indication to the registry. And I think we suggested that in February for the isotretinoin registry, not as a restriction, that if you didn't enter the right code you don't get the drug, but as

a way to evaluate how the drug is being used over time, and give us better information in the future.

And the second--to reply to Dr. Garner--I think a major difference in what they're proposing for risk management is that males and females who are not of reproductive potential would be allowed to have refills of this drug. And they're basing that on the psoriasis population. And I think that sort of deviation is not justified if the population is going to be largely acne patients.

DR. STERN: Dr. Schmidt.

DR. SCHMIDT: I don't want anybody to feel like I'm a diagnostic creep--

[Laughter.]

--but, you know, I really feel like we shouldn't dictate how to practice medicine. And I think a lot of these medications are going to be used, you know, off-label.

And I, for one, at least think that with--of course, you all also know my wife has really bad psoriasis, and is on methotrexate and Embrel for it. So I live with a women, you know,

who has psoriasis and still love her.

But I wanted to just say that I think we ought to increase the amount that people don't need prescriptions for this in males. I think seeing somebody with psoriasis, you know, every couple of months is maybe too much.

And then the other thing--and this may not be the appropriate time for this, but I think we need to think about this--is I want to make a couple of clinical reflections on retinoids, and how at least I treat people clinically, is I don't think the retinoids are the greatest thing in the world--you know, either Soriatane or Accutane, for plaque-type psoriasis. I think the best place to use the retinoids in psoriasis is the pustular-type psoriasis, or the acropustulosis, on the palms and soles, which can be devastating, painful, terrible, horrible. And they work beautifully.

But you don't ever leave anybody on anything, you know, for a long time. And when you do, the beautiful thing about the--at least the retinoids we have now, is you can decrease the dose

to where I have some patients who take one 10mg Soriatane every three weeks, and it keeps them clear.

So, a lot of these things you're not going to be giving them a real high dose, no matter what you're going to give them.

And then the other thing is, just like with my wife, you rotate people off, like methotrexate onto Embrel, onto something else, so then you don't have to worry about, you know, these side effects so much.

DR. STERN: Dr. Wilkerson?

DR. WILKERSON: AS a practicing dermatologist, I would plead--although it sounds like we've been siderailed by the patent office--in terms of having what I would call the "pan-retinoid" form. In other words, you know, right now, as it potentially stands, we can be scurrying to find five, six, seven, eight different forms for the particular drug and/or generic manufacturer, and/or sponsor making a drug. And since the side effects and the requirements are so

similar, a unified form would simplify, and I think would also increase compliance with things.

As far as the two to three month additional refills, I've sat here and debated that in my mind, also. As much as you want to see that from the standpoint of the patient's lack of not having to interact with the physician, it also yet provides another point of error at the distribution point, in terms of who gets--I mean, not to use any gender or similar names, but there are names and things where people could get refills that are females because of, you know, because the wrong box is checked, or an assumption's based upon a name that would result in females getting it.

And I think just like with Accutane, where it's monthly. It doesn't mean they have to have an office visit, but they have to pick up that prescription. To have two different systems, I think, is just introducing a point of error in the system well at the top which negates everything else that we're trying to do here, which is to reduce the rate of pregnancies.

DR. WALKER: I'd like to say that I think you've highlighted a lot of the controversy very well in what you've said.

As far as, though, distinguishing males and females, you wouldn't need to do it by the name. We've toyed with many different things. Certainly, the sticker program has you--you know, the physician fill out whether it's a male or female. We've toyed with a specific prescription pad that has male or females, and has, you know, basically like a gray box on it for females, which has the "no refills," and males are a different color, so it is clearly outlined.

But the pharmacist would not distinguish male or female by name, but rather by what is checked within the system.

Of course, a female of childbearing potential would also have the trigger of the pregnancy test, which is connected with her name. And each patient has a unique identified, which would force the pharmacist, the physician--everyone--to use that identifier and

check whether the pregnancy test has been ordered.

So there are safeguards for that aspect of it.

The one-month versus three-months versus more--it's very difficult--trust me, I have had the same thought--one system. The trouble with one system is they're not one patient type.

DR. WILKERSON: Right.

DR. WALKER: And this is a lifelong disease. I think you're going to take patients with psoriasis and you're going to put them on methotrexate, cyclosporine, acitretin or other biologics, because they can't come in--or afford it. The health care system can't afford for chronic cases to have them in there every month. It's very expensive.

DR. WILKERSON: Well, I mean, not to micro manage this down to that point, but, you know, there are ways around that. What I'm just saying, if you are designing a system, the less variability there is at each decision point, the less likely error is to slip in. And error will slip in,

regardless. But, just to make that easier.

And my other comment was: pharmacokinetics on this drug--I can't believe that everyone in this room, sitting here, has the same number of retinoid receptors in their bodies. I mean, do we all have the same number of retinoid receptors, and saturate at the same pharmacodynamics--

DR. WALKER: Well, there's a range from seven to 12 hours. So, no, everybody doesn't metabolize the same way, but that--

DR. WILKERSON: No, I'm not talking about metabolism, but in terms of once the receptor is bound, and there's a signal sent, does everyone have the same--in other words, it seems that picking a 4.5 mg dose is rather simplistic when we have 100-pound individuals versus 350-pound individuals. Their volumes of distribution and however else affects the pharmacodynamics of the drug, and what this leads up to is perhaps, have you correlated the weight of the individuals against your bone data? In other words, you know, are you seeing increased side effects in lower body

mass individuals perhaps?

DR. WALKER: We separated the bone--I'm want to kind of go from your last question and move forward. WE separated the bone data by gender and age, and we didn't see anything. But I don't know that we did it by body weight. They're shaking their heads no.

DR. WILKERSON: What you were trying to tell us before is there is no dose response.

DR. WALKER: Right. I am. And I'm going to show you--

DR. WILKERSON: --[inaudible] defies the laws of pharmacology.

DR. WALKER: I don't think it doesn't go with the laws of pharmacology. What it says is the drug is not lipophilic and it's not stored in fat; that it's actually in the plasma volume.

And I'm going to have my pharmacokineticist. He's got some very nice slides that I think will help you see this.

It is not changed by weight.

DR. YU: I'm Dale Yu, pharmacokinetics.

What we've done is we looked at the systemic drug exposure of tazarotenic acid, the active ingredient, as a function of body weight in the Phase 3 trials. And I will show you that data now.

Slide up, please.

[Slide.]

Okay, if I can focus your attention on the right panel of this plot, these are data from the two Phase 3 trials. We looked at drug concentrations from about 80 patients. The body weight ranged from about 50 to 150 kg, and the concentration on the vertical access, as you can see, over a wide range.

What we were looking for is some kind of trend, if there is a relationship between body weight and concentration, we should see either increasing or decreasing trend. And we were not able to see that.

So our conclusion that the drug concentration does not change as a function of body weight, therefore we don't need to consider dosing

by body weight.

DR. WILKERSON: Well, I mean, you're just looking at plasma concentrations here, right?

DR. YU: That's one of the things we looked at.

DR. WILKERSON: But you're not looking at efficacy--endpoint efficacy and expression of the disease as a result of your pharmacologic action.

DR. LU: So your question is whether we looked at efficacy as a function of body weight.

DR. WILKERSON: Well, dose response. I mean, it can be this, but it can also be what dose does it take to effect a particular response on the disease process.

DR. WALKER: we do have that data, and we'll share it with you.

DR. LU: John Lu, biostatistics, Allergan.

Slide up.

[Slide.]

A logistic regression was performed on data combining 048P and 049P study. The dependent variable was clinical success. And I regress these

covariates on clinical success. And we didn't find that weight was a predictor of clinical success.

DR. STERN: And what was the fit of the model?

DR. LUE: Umm--I didn't find a significant difference. I felt it fit pretty good.

DR. STERN: But, we need to know how well, in fact, each of these variables have any individual relationship. So a lack of correlation, in the absence of a model that has some predictive value, either says that you're looking at all randomness, or you've not chosen things in a way that, in fact, you have the right independent variables for the right dependent variables.

So I think--and your data sets--well, I just think it's hard to interpret.

But we'd better stop, in terms of one more-- DR. WILKERSON: One more comment. We've heard all day that this drug is like all the other retinoids. Well, all the other retinoids show a dose response curve.

DR. WALKER: Well, that's--yes. That's

because of the distribution. The distribute out of the plasma into the body fat.

DR. WILKERSON: Okay.

DR. WALKER: And tazarotene doesn't do that. It is, you know, a--

DR. WILKERSON: Here today, gone tomorrow--right?

DR. WALKER: Did you want to comment, Dr. Helms?

DR. HELMS: Just a point on the model, there.

Your point is a good point, but if you look at the significance level for the treatment, and the other factors that are significant, you see that the model really will pick up something that's important.

DR. WALKER: Any other questions?

DR. STERN: Dr. Ringel--and then we're going to take a break.

DR. RINGEL: Okay, I'm going to give poor Dr. Walker a break. This is going to be addressed to Dr. Trontell. And I promise there really be a

question at the end of my little speech here.

[Laughter.]

I really feel as if we're just taking one more step in opening up, you know, the Pandora's box of teratogenicity here. With isotretinoin, you give it to people for five months, and it has a spectacular effect.

For acitretin, I think very few physicians actually give it to women of childbearing potential, and that's probably why we've been saved from much of the teratogenicity of that drug.

On the other hand, we're talking about a drug here--tazarotene--which is going to be used indefinitely by women of childbearing potential. And that seems very frightening. I don't know how many women can use two forms of birth control and guarantee forever that they will not be pregnant. I think that's a very, very difficult task for anyone.

On the other hand, you know, if this were a really star-quality drug; if this were another Accutane for psoriasis, and it were just wonderful,

you know, then maybe it would be worth it. But it's not. At least not if it's like the other retinoids that I know.

And on the other hand--a lot of hands here--

[Laughter.]

--teratogenicity is very serious. It's a, you know, extremely serious problem. So, you know, you've got a risk-benefit issue.

I think Gloria Steinem--if she's here, please cover your ears--I'm wondering--here's my question: can we restrict this drug to males, and women who are not of childbearing potential? I think that that would solve a bunch of problems. I know it's not politically correct, but I feel that for the women and their future children, perhaps, you know, we need to take different steps for a different population.

There are drugs, for example--I mean, you know, there are things like Propecia that are indicated only for men. I mean, it has been done in the past. Would another risk-management option

be to restrict this to males and women who cannot have children?

DR. TRONTELL: Yeah, it's a tough question to think about the mechanism, how you would go about doing that.

If you tried to engineer some restricted distribution that would somehow knock out those individuals who are of childbearing potential, you'd presumably enter into a lot of complexities making that determination; is that an issue of, you know, anatomy and physiology or of behavior that defines your reproductive potential.

And I think the challenge gets at what was discussed by the committee earlier about our ability--or authority--to speak to off-label use of medication. So there are some products that are indicated for treatment of one gender versus the other but, in fact, that doesn't prohibit clinicians following reasonable practice patterns, and a belief that usual and customary--forgive me if not using the correct legal language--to employ them.

So I'm thinking, in practice it might be quite difficult to do what you suggest. In very exceptional circumstances, where there may be a unique indication, where the risks may warrant the benefits to the patient using the drug, has FDA ever even attempted to speak to the specific indication for which a product should be used safely.

DR. WALKER: Can I make one comment before--

DR. STERN: Dr. Bull was going to--

DR. BULL: you know, I think you have to go, also to--we try to make decisions based on data. And I haven't heard the committee comment on what I think is a disparity in the data base, and Dr. Cook's earlier presentation. It may have also been said in Allergan's--the disease has an incidence that does not reflect a male preponderance of the disease, but you're looking at studies that had about 80 percent inclusion of males.

Now, I don't know why that specifically

happened. But, in terms of the adequacy of the data to speak to female patients is also, I think, an issue we would welcome comments from the committee based on, you know, just what you see with regard to the demographics in the studies that have been submitted.

DR. STERN: I take the liberty of addressing that, as someone who's sort of followed clinical research in psoriasis for a couple, three decades.

And if you look at systemic agents, phototherapy, PUVA, and you look at the clinical trials published, one can predict that they'll be approximately two-thirds male, in terms of enrollment, across the United States and Europe, and they'll have a mean age of between 44 and 48.

So, whatever it is that goes into who gets enrolled, and trials of systemic agents, phototherapy and PUVA, over the last 29 years, there's a remarkable consistency about the profile of those individuals in psoriasis trials, including a fair number that are not part of NDA submissions,

but are just various kinds of clinicals done in academic or other institutions.

So, I can't explain it, but it's sure there.

Wilkin?

DR. WILKIN: I'd just like to comment on Dr. Walker's earlier statement about actions with FDA for the acne indication. And I think you represented that quite fairly.

WE were ultimately interested in a product--if it's a systemic retinoid and a teratogen--that it not be inferior, efficacy-wise, to isotretinoin. And the committee has picked up on some of our concern that was in our portion of the briefing document that went to the committee. We referred to the posters from Allergan, presented at the American Academy of Dermatology, and also some of the articles that show up in the throw--the journals that come for free--

[Laughter.]

DR. STERN: I think we call them "non-peer-reviewed."

DR. WILKIN: Non peer-reviewed. That's better than what I was actually going to say.

[Laughter.]

And this is actually the summary paragraph from one of these: "Nodulocystic lesion count data also show a statistically significant benefit for both tazarotene 3 mg and 6 mg compared with placebo. Allergan has completed Phase 2 studies in the treatment of nodulocystic acne, and is currently seeking a partner in the United States and Europe for further clinical development."

So this is something that a lot of dermatologists would get to read.

And I'll not read all of the posters, but just one of them. It says: "The results in this early Phase 2 trial show that once-daily oral tazarotene, 3 mg or 6 mg, reduces the numbers of both non-inflammatory and inflammatory lesions. It efficacy against commidones is especially notable, since these lesions are the precursors of inflammatory lesions. Oral tazarotene could prove to be an effective new therapy for patients with

acne, and further investigation is warranted."

So these are a whole series of posters that were presented at the American Academy of Dermatology.

DR. STERN: Thank you.

And why don't we take an eight-minute break and come back at three o'clock.

[Off the record.]

DR. STERN: Back on the record.

We'll have one final question, from Dr. Furberg, and then we'll move on to the questions.

Dr. Furberg.

DR. FURBERG: Well, I ha two brief comments and a question.

One comment relates to bone mineral density, which we are using a surrogate for fractures. And my view is that there are no good surrogates. And bone mineral density is certainly not. And the fact that there was no good relationship between bone mineral density and fracture doesn't mean anything to me.

There are treatments that increase bone

density, at the same time they increase risk of fractures. That's just an illustration of how weak that is.

So if you're going--what I'd like to do is to encourage you to use fractures as an outcome in your future studies, and not rely too much on bone density.

The second comments relates to the whole issue about pregnancies. And I was surprised to hear that there were 113 worldwide exposures. And most of that information came from you. And for 107 of them, you have either "no adverse outcome" or "unknown."

And that, to me, is terribly disappointing; that you're lumping the two--you're lumping the two, "no adverse outcome" and "unknown." I mean, you should cut down the number of--first of all, you should separate that, and the unknown should be down to zero.

DR. WALKER: I'm not sure I understand; 102 what?

DR. FURBERG: Pregnancies.

DR. WALKER: We didn't have 102 pregnancies--

DR. STERN: Topical taz--that's what you indicated.

DR. WALKER: We had eight pregnancies.

DR. STERN: No, in topical tazarotene.

DR. WALKER: You mean, yes--

DR. FURBERG: What I'm reacting to is the fact that you are not doing more to eliminate the unknowns in your data base. I mean, this is a critical issue for us to know. And so I'm expressing--this is a comment. I'm expressing my unhappiness.

The question I have relates to hyperglycemia. You had seven events. And I just wonder whether the drug is causing diabetes--we didn't hear anything about that. And, if so, whether that should be part of the labeling.

And, second is: whether, if it has an effect on glycemia, whether it should be used in diabetics?

DR. WALKER: Okay.

DR. FURBERG: That's my question.

DR. WALKER: All right. Number one, the pregnancies--those are spontaneous reports that come in. WE actually track every report we can. But sometimes they come in, not from a doctor, not even from the person who's pregnant. So we track them to the best of our ability, because they come in spontaneously in the field from multiple different sources.

So, I agree that it's unsatisfactory, but with the systems that are in place for surveillance, we always do the best we can do, and we take those very seriously. But, I agree, they're not to anyone's satisfaction.

The second point, being the hyperglycemia--and I'd like to have a slide up so I can address that.

[Slide.]

There were seven cases of hyperglycemia, called an adverse event by the physician. That is just what the physician determines to be an adverse event. Those were in the double-blind studies--the

048, 049P studies. There were none in the placebo.

But what I think is more important to look at is not the number of adverse events which were called that by the physician, but what the incidence of hyperglycemia was in the whole population. Because I think it's just--the 2 percent is not really real.

If you look, the 14 percent of the patients--or almost 15 percent--had elevations of hyperglycemia in the tazarotene group; 18 percent in the placebo group. So when you look across the population, you really didn't see that.

DR. FURBERG: Well, I disagree with you on that. I'm interested in the rare cases, where a drug may induce diabetes. And I don't expect that to happen in everyone. It's just a small group of people that are susceptible. And you have seven to zero. And I'm saying I'm not satisfied with you classifying them as "hyperglycemia." I'd like to know more about those. You should go back to the case records.

Were those patients diagnosed as

diabetics?

DR. WALKER: They were--

DR. FURBERG: Started on treatment? That's what I'm asking.

DR. WALKER: Actually, the patients were diabetic. They were on treatment, often because they come in for the labs fasting. They do not take their hyperglycemic drugs.

The patients--if you look at the scattergrams at all the time points, there are no differences between the groups. And patients go up and down.

So we didn't see any trend. We didn't see any one-off's, we didn't see ones that popped up high. So we did not see a signal. All we saw were that some physicians--it turned out, seven physicians--called the hyperglycemia an adverse event. When you have a laboratory abnormality, the investigator has a choice whether they call it an adverse event or not. And in this case, they fell into the tazarotene group.

We've looked very closely at the actual

lab data and don't see that.

DR. FURBERG: I wish you had presented those seven cases so we could--we could take a look at it.

DR. WALKER: Okay. And I don't have those seven broken out.

DR. STERN: We're going to now end the question period, and go on to the questions to the committee.

So I'd like to thank Dr. Walker, because unless there is something extremely pressing, I think--you can now relax and enjoy--

DR. WALKER: I'll be very--you know, there is one thing pressing. I think that there's been a lot of discussion--

DR. STERN: I'm sorry. I'm going--I think I'll have to take the--we only have two hours left, and we have five questions, many of which have subsets; some of which are just for discussion, others of which are for a formal vote.

The first question, which is two parts, the first part is:

"Based on the information from the clinical studies conducted for tazarotene capsules, is there adequate demonstration of effectiveness for moderate to severe psoriasis?"

This is for discussion. And so I think what I'd like to do is go around the table, for people to make comments--or not, as they so choose--as to whether they believe the clinical studies presented here, and given to us, in fact show that this is a--quote-unquote--"effective for moderate to severe psoriasis."

And, perhaps--Dr. Honein, could we start with you? And a "pass" is fine.

DR. HONEIN: I pass.

DR. STERN: Dr. Furberg?

DR. FURBERG: Yes, but effectiveness, for a chronic condition, you don't show in 12 weeks. So its effectiveness--I would call it short-term.

DR. KATZ: Not to parse words, like the famous "is"--what does "is" mean?

[Laughter.]

But "effectiveness"--effectiveness or not?

Yes, I think it's been demonstrated that the drug is more effective than placebo, for moderate to severe psoriasis. Now, would you translate that to quote somebody as saying "it's an effective drug?" If you define effectiveness as better than placebo, I would modify my response by saying, it's better than placebo.

DR. STERN: That sounds like a low pass.

[Laughter.]

DR. KNUDSON: I'm going to echo what Dr. Katz said. Yes, it is more effective than placebo, but that's about the best I can say.

DR. STERN: Dr. Sellers?

DR. SELLERS: I have problems also with the term "effectiveness." I would say that it showed some efficacy. But with the background materials that we were presented with other treatment modalities, it does not represent a significant advantage over currently marketed drugs.

DR. STERN: Dr. Schmidt?

DR. SCHMIDT: Yes, I agree. But--and, of course, I'm looking at this through the filter of

my clinical experience. As I said before, I don't think any of these retinoids are just real start quality for plaque-type psoriasis. But I would almost bet you a million dollars this is going to be great, you know, for other forms of psoriasis.

And then the other thing that really is a mitigating factor for me, is the short half-life with this stuff. I mean, to me, to have a retinoid, you know, that washes out of your system, and you potentially can give it to younger people for some of the sever acropustulotic-type psoriasis, I fell like, you know, this is going to be effective for us.

DR. STERN: But we haven't seen any data on that.

DR. SCHMIDT: No, I said--

DR. STERN: Right.

DR. SCHMIDT: --I've got this clinical--

VOICE: Feeling?

DR. SCHMIDT: --feeling.

[Laughter.]

But I agree with what was said. What

we've been presented--

[Laughter.]

DR. STERN: Dr. Raimer.

DR. RAIMER: Yes, I think I have to go on the side of being effective. If you can see at least 20 percent of people clear or almost clear in 12 weeks, I think you have to call that--for all the drugs we have for psoriasis, that's at least somewhat effective.

DR. EPPS: I agree with the comments so far. I agree I was a little disappointed with the 20 to 30 percent, but it has shown more than placebo.

DR. HOLMBOE: I agree, I think it's mostly an efficacy issue, not an effectiveness issue. Also, I'd like to make a couple other points.

I think one caveat, in looking at this data, is we don't know the reliability and validity of this OLA tool. And that worries me a bit. And I would have liked to have seen more information about the tool used to score.

However, that having been said, if you

look at the number needed to treat, the number you need to see effect is seven to eight. So you think when you look at some of the things we use in other conditions--putting aside for a moment our concerns about teratogenicity--that's not a bad number to treat. So I think it has shown some efficacy related to placebo.

MS. SHAPIRO: I think Eric's last point is compelling, and I will defer to the rest of you on that.

DR. RINGEL: I basically agree. I think without a valid--without an instrument that's been validated, without knowing exactly how this OLA was performed, and how reliable it is, it's very difficult to say if this is an effective drug.

However, listening to the people presenting their data, and knowing how retinoids work in general, I would suspect that it probably is an effective drug.

DR. STERN: I think the data suggests, at best, modest effectiveness. In this clinical development program of 700 patients, and we saw the

best photographs that--when I treat people with narrow-band UVB, would make me wonder about whether my lights were up to full power.

DR. GARDNER: I'll defer to my dermatologist colleagues.

DR. WILKERSON: Yes, for efficacy. And it fills--I think Dr. Schmidt's point is well taken, and something that hasn't been talked a whole lot about is that female bracket--who the other retinoids are out of the question for--this does--and I think that's the most compelling reason to approve this drug is for that niche of females who need a retinoid, who don't respond to any other therapy, and want to get pregnant in the future. Right now, that's really not a possibility with the others on the market right now.

DR. DAY: Better than placebo; maybe better but can't tell, given the current level of data.

DR. LEVIN: Yes, with all of the limitations that have been expressed by others.

DR. STERN: Well, that was easy. [Laughs.]

Now to the second part:

"Is there adequate demonstration of efficacy for 'very severe' psoriasis?"

And perhaps, Dr. Cook, can you quickly put up your slide that broke out--just to remind people that the proportion of individuals with "very severe" at baseline who cleared was not significantly, but was only in the placebo group, is my recollection.

DR. COOK: Dr. Lee can put that up.

DR. STERN: Oh--sorry.

DR. COOK: No problem.

[Pause.]

[Slide.]

DR. LEE: Here's the subgroup results of treatment success for the first study. You take a look at the last row; basically break it down into baseline, disease severity.

So the highlighted part--the very severe--there were a total, in the first study, only five patients enrolled. And the two patients treated with tazarotene did not achieve treatment success.

[Slide.]

This is the result for the second study. And, again, the last row, a total of 10 patients enrolled in this study. And four patients were treated with tazarotene. And, again, none achieved treatment success.

DR. STERN: Should we go around and start with Dr. Levin?

DR. LEVIN: I would not see this as an approved indication.

DR. DAY: And what question are you wanting us to comment on at this time?

DR. STERN: Is there adequate demonstration of efficacy for--quote-unquote--"very severe" psoriasis. That's why I had that slide put back up.

DR. DAY: Right--because the indication is--for--I understand, but it does say "moderate and very severe." So we're just commenting on "very severe."

Yes.

DR. STERN: That there is demonstration of

efficacy for "very severe." They went 0 for 6, I believe.

DR. DAY: I'm sorry. Why don't you consider around this way, we'll come back.

DR. WILKERSON: yes, the data is obvious. But I would point out that the metric here is--if you take somebody with 90 percent psoriasis, and they had to get almost to "clear" or almost clear, in the real world that rarely happens. But that patient may very well have improved, you know, 60 percent and still be happy with the results.

So, yes, based upon the data--but I don't like the metric that we used in this particular study. I don't think it's as flexible. Even a POSI has its problems.

But, as far as the data and the endpoints, the answer is no. But in a clinical sense, it probably did make a lot of people a lot better. They just didn't hit that magic clearing point, which is probably unrealistic for somebody with very severe psoriasis in most cases, for any therapy.

DR. GARDNER: I think the answer to the question is no, but I would have to defer to others about the subtleties.

DR. STERN: I think the answer is no, and I think the reason it's important is: if it were labeled for "very severe" that would be a relatively unique labeling for psoriasis product, and it might well be that people went in with expectations--both doctors and patients--of a level of efficacy for the most severe cases, beyond which is supported by the data.

So I think it's sort of part of keeping the prescribing playing field as level as one can, in terms of information that's in the insert. And it certainly would restrict people from using it when they thought, "Gee, this person's--"--whatever, and might be susceptible.

DR. RINGEL: I don't think I have anything to add. No, I don't think that it's justified by the data.

MS. SHAPIRO: I agree with Dr. Stern's comments.

DR. HOLMBOE: I agree with the above, and even if it had shown some efficacy, there wouldn't have been enough power here for me to be convinced one way to the other, given there's only a total of 15 patients who had the "very severe" in both 048 and 049.

DR. EPPS: I agree also. It would be hard to achieve minimal to no psoriasis within 12 weeks.

DR. RAIMER: I agree. No further comment.

DR. SCHMIDT: No.

DR. SELLERS: No.

DR. KNUDSON: Also no.

DR. KATZ: No.

DR. FURBERG: Yes.

DR. HONEIN: I agree, particularly with the power comments, for trying to assess this.

DR. STERN: Gee, if it had gone 6-for-6, versus 0-for-7, I would have taken it.

[Laughter.]

But I'm not a biostatistician.

Ahh--the next questions also for discussion, are divided into two parts. They both

have to do with "has the safety profile for this product been adequately assessed?" And the first is:

"Please provide discussion of the clinical and preclinical safety data, including comments on bone and liver abnormalities, hyperlipidemia and teratogenicity."

And the second is:

"Please discuss any potential issues regarding long-term safety of oral tazarotene with repeated use."

And I would ask everyone not to reiterate their concerns, which are on the record, but really to try to use the time to bring out something that they don't think either they or someone else has addressed for each of these two.

DR. HONEIN: I'm concerned about the pregnancy rate that was observed in the clinical trials. And I'm sort of not comforted by the explanation that they didn't do a thorough education campaign as part of the clinical trial, because I don't understand that--and even three or

four years ago, how that would not be warranted.

And the other issue with respect to the sort of off-label usage, just wondering if the plan to have multiple dosages of this is going to make it easier for off-label usage, or if there's another rationale.

DR. FURBERG: For bone, there was a trend for fractures, which I think is more important than bone mineral density. So, inadequate power to evaluate that possibility that this may be real.

For hyperlipidemia, we didn't have a good discussion on that. We didn't get good presentations on how many people had increases, exceeded the treatment guideline goals.

And for teratogenicity, incomplete ascertainment. We are missing information on known cases.

And so, overall, I would say the safety profile for the product is not adequately assessed.

DR. STERN: Dr. Katz.

DR. KATZ: The question being "Has it been adequately assessed?"--and I think it has been

adequately assessed, given the time limit of 52 weeks, as well as could be.

However, the discussion of the safety data that my comments on bone is very worrisome. Everything's in the same direction: decreased bone density, patients' having symptoms of musculoskeletal symptoms, an alkaline phosphatase--all in the same direction.

And these are the objective things. These are not subject to double-blind , non-double-blind things. These are the same.

Liver abnormalities--I think we are reassured. And hyperlipidemia would not bother me. First of all, it's a controllable problem. We worry, as clinicians, about things that are not controllable, like increasing osteoporosis that you can't reverse. But hyperlipidemia, if you get adequate lipid assessment--though the one case bothered me. But that patient probably, in a clinical practice, wouldn't have happened because started with a high triglyceride and it kept going up. And somehow the drug was continued. The

patient ended up with pancreatitis in the hospital. I mean, I can't imagine that that would happen in clinical practice. And so that wouldn't bother me.

And the teratogenicity is obvious bother. And we spent time discussing the limited--the risk management.

As far as the second part, potential issues are bone--bone, which is paramount; and obviously the pregnancy in patients--unlike the Accutane, where we're concerned about this, people using it for 20 weeks. People could be using it for a lot longer than 20 weeks with this.

So that would be of great concern.

DR. KNUDSON: I'm so glad that Dr. Katz comes before I do.

[Laughter.]

He said it just beautifully, and articulated for me the things that I've been thinking. Yes, I agree with him.

DR. STERN: Dr. Sellers.

DR. SELLERS: Yes. I just would reiterate again the problem with power. When we design

efficacy trials, we don't really have the best statistical sample for evaluating safety.

Also problematic is the length of follow-up, and the demographics, again, because we have more males in the study than females. And we wonder to what extent we're excluding populations that may be at risk for some of these observed effects that we're seeing.

So I would say that the safety profile has not been adequately assessed.

DR. STERN: Dr. Schmidt?

DR. SCHMIDT: I think there's no doubt about the teratogenicity. As far as the hyperlipidemia, I think that's been assessed.

Liver abnormalities, to me--and liver chemistries--I hate to say it, but I don't do GGTs and some of these other things. But I'm not going to--I feel like they have assessed that.

And the only thing that's really troublesome to me is this bone. I don't think that's been, you know, really assessed. And it's unfortunate that, you know, musculoskeletal pain,

and then bone pain--like in renal patients--to me is different. You know, and I wish we had gotten more information on that to make--but I agree, I don't think we have the numbers for that.

DR. STERN: Dr. Raimer.

DR. RAIMER: Well, I think triglycerides could be a potential problem. I don't necessarily think the drug is potentially raising the triglycerides too much, but 2 percent of the placebo patients had triglycerides over 500 to start with. So I think the company was not planning to recommending any lab, but I think a screening triglyceride to prevent people from getting pancreatitis wouldn't be a bad idea.

And maybe considering if somebody's on the drug for 12 months, recommending DEXA scans--at least for a while, to follow bone densities, until we're sure it's not going to be a problem--and numbers of fractures.

DR. STERN: Dr. Epps?

DR. EPPS: I agree that the--I don't believe it's been adequately assessed. The only

thing I would add to all the preceding comment is regarding the hyperlipidemia. And, I guess, 41 percent was the number that I did see at one time. And my concern, in young adults and, you know--people, young people who are living a long time with the disease, or with the potential to take this medication, really cardiovascular and long-term side effects, and whether or not those were seen. And I didn't really hear much about that.

DR. HOLMBOE: I agree with basically everything's that been said previously. The only thing I would add is that I would encourage the sponsor to think about the way it's measuring some of its adverse events--getting back to Dr. Furberg's point of kind of these self-report things, without better clinical definitions of exactly what we're looking for, such as things like diabetes and other endpoints.

MS. SHAPIRO: As a non-medical person I'd again defer to you on this, although what seems poignant to me, listening to you, is the length of

time that this drug is potentially going to be taken, versus the drug we dealt with last time.

DR. RINGEL: Likewise, I agree with the previous speakers. The only points that I have that are different, first of all, has to do with the issue of semen. I found--

DR. STERN: We'll get to that.

DR. RINGEL: Oh, I'm sorry.

DR. STERN: We have questions about that later on.

[Discussion off mike.]

DR. RINGEL: I will save that.

In that case, briefly, the alkaline phosphatase has been elevated and, intermittently, AST and GTT are elevated. And, to my mind, it's probably from bone, but it could be from cholystasis, too. I think it's unlikely, given what retinoids have done, which has usually been hepatocellular problems. But I think that fractionating that alkaline phosphatase makes a whole lot of sense, and some sort of mandatory Phase 4 study, you know, fractures--at the very

least--if not some other non-direct measurements of bone metabolism.

DR. STERN: Dr. Garner?

DR. GARDNER: Nothing to add.

DR. WILKERSON: Well, as usual, I do.

[Laughter.]

Yes, I think the side effects of this drug are manageable, but I think the package labeling should include recommended or suggested guidelines. I don't think this is a drug that should be put out there on the market--I mean, when we look at isotretinoin and how long it took to realize that it caused depression and some of the other, you know, adverse events. I mean those are one in 20, one in 50,000-type events. We need to be vigilant beyond spontaneous reporting.

So, I don't think patients ever get upset about having some blood work drawn that protects them. They get upset when things happen and we haven't been vigilant--whether the package labeling indicates so or not.

So I think all these things are--we've

been dealing with this for years, retinoid side effects. They are easily dealt with with appropriate monitoring.

DR. DAY: I agree with the previous speakers. I wish more had been told to us about the possibility of an on-and-off course of treatment, because we don't know anything about the very, very long use of this product.

DR. LEVIN: I guess I agree with the previous comments. I just want to point out that what's being said here really makes Question 6 extremely important, about additional studies, and would they be needed, prior to after approval.

DR. STERN: We'll go on to one of two questions that we've be asked to vote on. I guess this is sort of generally the question at these meetings, which is:

"Give the safety and efficacy information, does the committee find a favorable balance of risks and benefits which would support approval of this drug?"

And I think that means "at this time," on

the basis of the information we have, since, as you pointed out, there's Question 6.

And I'd like to take the opportunity to make a comment: is that unlike the sponsor, I believe that in deciding--one of the nice things about being only a special government employee for a day, is one has a greater latitude to think--as that trite phrase is--outside the box, or outside the box-labelings, in this case, and think about what happens to the public health when a new product--one's best estimate of what is likely to happen to the public health when a product is approved for a given indication.

And, therefore, I think we have to think about how responsive we thought the sponsor was in terms of some of us who had concerns about off-label use, and minimization of that, in decided about benefits and risks from a societal perspective, and not as if this product would always be used within the indication.

So that more global perspective--in the absence of more reassurance, either about dynamite

efficacy for acne, or knowing about it very soon, or an extremely robust program to make sure it's not used widely in people at high risk for becoming pregnant, where there are alternative drugs that are at least, and perhaps more, effective for that indication with similar risks makes me vote no.

Dr. Levin?

DR. LEVIN: I would vote no, too.

Abstain.

DR. WILKERSON: I would vote for approval of this drug, with monitoring, and a Phase 4.

DR. GARDNER: I guess I would answer the question, no, but want more discussion about modification.

DR. RINGEL: This is a less toxic drug Soriatane, but the issue of teratogenicity and its effect of society, and everything we have learned from Accutane over the last 20 years is so compelling, that I would have to vote no at this time--until that issue is settled.

MS. SHAPIRO: I guess I need clarity on the question. Is this with a risk-management program

that I still don't completely understand--or not?

DR. STERN: Ahh--I think this is with the risk-management program--

MS. SHAPIRO: That's been--

DR. STERN: --that one would presume, at the individual level, was of equal efficacy to that we hope will soon be in place for other retinoids.

I think, in my deciding on that, I thought the risk per exposed individual of unintended exposure during pregnancy, correcting for that person's demographics, would be the same. And my concern, really, is on the benefits side, where the teratogenic risk is, in a population sense, is in the acne population. And I don't know if the benefit's equal.

So--and my concern is that it will be largely--or to a large proportion--used with less benefit, with equal risk, which is the logic behind my vote.

MS. SHAPIRO: But if the risk-management program were comprehensive enough, it might answer some of your off-label concerns.

DR. STERN: No. If you have two drugs, each of which has a risk your really worried about--let's say, two drugs that have a one in a thousand risk of instant death, and one of them works--and the risk of death is proportional to how long you're on it, or how many courses you have; and one requires more courses or a longer period of time--

MS. SHAPIRO: Mm-hmm.

DR. STERN: Even for that low risk, you wouldn't want the other drug on the market.

MS. SHAPIRO: Right.

DR. STERN: And that's the logic behind my vote.

MS. SHAPIRO: Okay. With that, I abstain.

DR. HOLMBOE: I don't feel I can answer the question at this time until I know exactly what the risk-management program is going to be, and what additional studies are planned.

DR. EPPS: The question, given the safety and efficacy information presented--my vote is no.

DR. RAIMER: I vote yes.

DR. SCHMIDT: I vote yes.

DR. SELLERS: Based on the overall public health benefit and burden, I vote no.

DR. KNUDSON: I vote no, because there's too much unknown.

DR. KATZ: Before my vote, I just want to say that, obviously, when it comes to efficacy, it works great--for some people. The need is there--we agree. And biologically, it's exciting.

But it's not very efficient. With the numbers we've seen, 17 percent--and then numbers were given, "patient satisfaction," 75 percent. Let's not forget about placebo of being 50 percent. So, with all the problems involved, and the low general efficacy, my vote would be no.

DR. FURBERG: My view is mixed. I think in a highly selected group, with a risk-management program, the drug may be okay. But there's a lot of missing information that could open the indications more broadly.

But I'm with Eric, that I think we need to hear a little bit more about what would be the

risk-management program before I sort of finally support approval for a very limited indication.

DR. HONEIN: Based on what's been presented so far, I'd vote no.

DR. STERN: We need--Dr. Furberg, we need "yes," "no" or "abstain."

DR. FURBERG: Abstain.

DR. STERN: Now we get on to a three-part question, parts of which are for discussion, and the third part for a vote.

"Allergan has submitted a risk-minimization--"--and, actually, I'd like to ask the FDA, since there has been substantial progress and evaluation of risk-management program since the original packet, whether they wanted to perhaps modify this question, in terms of parts A and B, since at least part B--it's my understanding that the sponsor is now going to require--proposing a requirement for all people to whom it's prescribed, independent of gender or risk of being pregnant. And there's been other evolution.

So do want to change A and B at all? Or

do you want us to still address them?

DR. BULL: Well, I think in terms of general principles for a risk-management plan, I think we've heard a fairly consistent message from around the table that it would be--you'd like to see a consistent program across all the retinoids; and that the same kinds of risk management--given that there's high probability that this one is an equivalent teratogen to the other products that are currently marketed--I guess if there are any additional comments that are consistent with any other concerns that you want to be sure the agency attends to, maybe that might be the most useful to us for A and B.

DR. STERN: Great. Do you want to start, Dr. Levin?

DR. LEVIN: I--what am I voting on?

DR. STERN: As I understood Dr. Bull--and please correct if I'm wrong--that there's been a general sense, which is also my sense--that the committee--or many members of the committee have felt that a standardized program across teratogens

[sic], however it best evolve, would be applicable to this agent, as well, if approved. And I guess the question--the comments the FDA might like are any disagreement with that general principle, and any particular advice that's come out specifically at this meeting, and not revisiting the February meeting at all.

DR. LEVIN: I would agree that, both from the perspective of reducing burden, and the opportunity for error, that standardization is sometimes a good thing.

I would encourage the agency to talk to sponsors about the appropriateness of including indication for tracking how drugs are used, and not just relying on marketing data.

DR. DAY: Some standardization would be very helpful for the reasons that Dr. Levin has said.

I can't tell enough about the materials in the briefing document about the risk-management program. For example, there are different brochures for males and females. And it could just

be that males have less information, so some things are left out. But we haven't discussed the other question, about the involvement in males, so this gets a little bit circular, to decide all of these things.

So, in general, a general program that would be appropriate for all drugs in this class would be nice, but sponsors should be allowed to come forward with specific exceptions, given their product--such as the half-life in the body, and so on and so forth.

DR. STERN: Dr. Wilkerson?

DR. WILKERSON: Like I said before, I think the pan-retinoid form, from the practitioner's standpoint, is the best way to go with this, for lack of confusion, and just everything else in the market. And then--you know, it's hammering out the details. But to have seven or eight different renditions of managing these drugs, for practitioners is just a nightmare.

As far as the indication being on the scrip, my only concern about that is since we do

have to use drugs off-label many times, that it not become a means of an insurance company denying coverage for a drug that a patient needs because it's not--quote--"the FDA indication," which is a continual problem with insurance companies, is that they tend to cling to these indications when, in fact, we all know we use drugs off-label every day.

DR. GARDNER: I think I'd like to pass on this until we get to the discussion of the male involvement.

DR. STERN: Nothing to add?

DR. GARDNER: Nothing to add at this time.

DR. RINGEL: I'll pass, as well.

MS. SHAPIRO: Nothing to add.

DR. HOLMBOE: I would simply reiterate what Dr. Furberg had said earlier about some sort of feedback loop in this program. There's a lot of monitoring activities that appear to built in, but there doesn't appear to be any feedback, particular to the practitioners.

There is good evidence now in the health services research arena that feedback, particularly

when it's physician-specific, can change behavior. And I think that would be really important to include.

And I'd also like to see more active involvement on the part of patients. There are also techniques, such as getting patients to write down a commitment to adhere to a program can also increase compliance rates. And I think those should be considered as well.

DR. EPPS: I like the idea of some kind of standardized program. Currently, we have many different pamphlets and folders and things to distribute and have signed.

The other issue--although that's admirable for patients to write things down, sometimes they'll put down what they think you want to hear. So, I mean, that's just being realistic. And I'm sure the sponsor would go along with whatever FDA recommended.

DR. RAIMER: I really don't have anything to add. I'm still not sure why we include males in a registry, but I do like the idea of having it

standardized, however we do it.

DR. SCHMIDT: I agree.

DR. SELLERS: I agree with the previous comments, and I also strongly urge the use of indications within the risk-management program, because although clinicians and professionals are generally aware that off-label use occurs all the time, in many cases patients and consumers don't realize that the drugs they're being treated with have never been approved for the indications in which they're being treated.

And so we'd like to have that information available.

DR. KNUDSON: I'm extremely disappointed that after the February meeting we're still hung up on getting a standardized program. I thought we had decided that there would be.

I would like to urge the FDA to please find a way out of this patent problem. There must be a way to solve that, and solve it fairly soon.

DR. KATZ: I have nothing to add.

DR. FURBERG: Nothing to add.

DR. HONEIN: Nothing specific to add, but just to reiterate support for a standardize program that would be easier for all elements to follow. And I really do see a benefit of indication, and I don't know that there's a way this can be part of the registry without insurance companies' having access to it. I would think privacy concerns might be able to get around some of this. But I think it would be useful, both for the feedback to providers, and for evaluating the programs.

DR. STERN: thank you.

With the Executive Secretary's permission, the next thing is for a vote. And it has to do--it's the question of: "Are the scientific and clinical uncertainties surrounding semen levels of Tazorac--the metabolite of Tazorac--a factor to be considered in tazarotene risk minimization?"

And I don't know--is it possible to do 5, 4 first, because that's really the factual basis.

MS. TOPPER: You may.

DR. STERN: So, why don't we do 5, which is the discussion basis for then voting--I think.

So, Question 5, again, three parts, all for discussion:

"How can FDA best address the potential clinical relevance of high tazarotenic acid levels in semen? Options might include: A) further delineation of the potential risks (via consultation with teratogenicity experts, additional preclinical studies, etcetera); B) informing clinicians and patients of the finding and its uncertain clinical relevance; C) recommending precautions (such as the use of condoms) pending characterization of the potential risk."

And we're asked to "Please comment on whether further risk assessment should be done, and whether any cautionary language or recommendations should be made while additional risk assessment is pending."

Who would like to--Dr. Honein.

DR. FURBERG: I'm for A, and I would like to add "D"--additional studies. That's really what we need. Right now we don't know the significance

of the changes.

DR. STERN: Dr. Katz?

DR. KATZ: Well, why wouldn't these concerns be alleviated by just having a labeling, just like females can't get pregnant for one month, having males use the same precautions for a month afterwards. So, in other words, having C cover everything.

Is that not feasible, or am I missing the point?

DR. STERN: I don't know. I mean, I--I'm no surer about this than I think I'm hearing you are about this.

DR. KATZ: It's got to be--half-life is seven to 12 hours. Do we--is it appropriate to ask if there's data on how--

DR. STERN: Dr. Wilkin?

DR. WILKIN: Yes, just--a point of explanation on the query here.

One of the daily challenges that we have at FDA is taking some evidence of a potential risk, and then translating what we know into wording that

goes into labeling. And we're always trying to get it just right. We don't want to over-warn, we don't want to under-warn. If there's uncertainty, we need to convey that. And even though it's a daily task, it always seems to be something that we need to spend a lot of time and a lot of thinking on.

And I guess that's what we're asking you to share that piece with us.

If we end up over-warning on this part, what we might end up with is labeling that said, you know, "You absolutely must--"--and if we don't have other pieces in the labeling, then women who otherwise had a pregnancy that was very highly desired, they may have this concern and have a termination based on really scary language.

So I think that's--you know, we're trying to hear from the advisory committees, in this case, you know, the direction that we should pursue here.

DR. KATZ: I appreciate that comment. And, with that in mind, probably, either we should--if they have the data, we should see that

again. I know it was very lucidly given to us by the sponsor. But perhaps we should see that data.

I remember some astronomically small--one out of--

DR. STERN: One in 5,000.

DR. KATZ: --5,000 number. But from other toxicologic studies, can that ever be significant?

So I think we would need to have more information before we answer that question--at least I would. Maybe we could see the slide again, if anybody else would like to.

DR. STERN: Why don't we see the slide that showed the 1 in 5,000--an FDA slide.

DR. BROWN: My name is Paul Brown. I'm acting pharm-tox supervisor in the Division of Dermatologic and Dental Drugs. And we anticipated this question might come up, so we actually have a backup slide that addresses some of these issues.

[Slide.]

The slide you saw before had this information in it, and I believe that the total dose that could be achieved in semen--assuming

worst-case scenario--would be about 831 ng, which about 1/5000th of a single 4.5 mg capsule dose.

To try to put that in perspective with the teratogenicity studies, it's about 1/6000th of the highest oral dose that was not teratogenic in animals. So that would be a no-AL.

This last bullet just sort of goes over some of the uncertainty about that information; that, as Dr. Yao presented, the human may actually be a more sensitive species than some other animals.

So, looking at other retinoids, you see a ratio that might reduce that 1-to-6,000 to something else, and just using the numbers that are available for the other retinoids, you might reduce it to some of the numbers shown there.

That's just based, again, on the literature and information with those other retinoids. We don't know for tazarotenic acid.

The other uncertainty, of course, is that the semen would be delivered by the vaginal route. The teratogenicity studies are oral studies, so we

don't really know whether you could get greater exposure to the fetus from the vaginal route than through the oral route. There actually is some evidence in literature that that is possible; that you can get higher exposure in the uterus by the vaginal route compared to other routes.

So, again, the margin of safety might be reduced even more, and it's just uncertain at this point.

DR. STERN: Am I correct that the greatest concern would be, in fact, with exposure after implantation, essentially; or after fertilization by prior intercourse, as opposed to anything to do--some of it might be mitigated by some kind of a warning of using only--"If your partner becomes pregnant, then use a condom--"--as contra-logical s that may sound.

[Laughter.]

DR. BROWN: Yes, I think there's two--[laughs]--I think there's two possible areas where there could be risk; either it's exposure initially, at conception--you know, what with the

tazarotenic acid in the semen at that point; or repeat exposure later.

And there are fertility studies that looked at teratogenicity when male animals were treated only, and they didn't really see a teratogenic signal at that point. So I think the main focus has been exposure if there was repeated exposure, once a female's pregnant.

DR. KATZ: Well, with that information, I would think, until any further data comes up, then we have to have some labeling as far as the male goes.

DR. KNUDSON: Well, A, B and C all seem very reasonable to me--plus D, as Dr. Furberg said. But I will defer to others.

DR. SELLERS: It sounds like we have an incomplete risk analysis, and that further animal studies are necessary to understand what the dose is at the target, and what the effect of exposure duration may have.

DR. SCHMIDT: I think this is a real sticky wicket, in the sense that one of those slides up

there said that this was like 10 cc of semen. And I don't want to belabor that point, but all I can say is, "What a man!"--you know?

[Laughter.]

But--seriously--you know, these are such infinitesimal amounts, and I think that B, informing clinicians and patients of findings--[laughs]--this is--and findings, and its uncertain clinical relevance would be the thing that I would put down.

I think that when you have 11,000, six times the lower the amount to produce in animals and this other stuff, I think this is something you are--you're going to create more problems.

And I know why we did this is because of the problem with Accutane, and some of the teratogenicity. But I thought that was not really proven.

DR. RAIMER: I agree, at this point in time we seem to have no idea of whether it's a problem or not. But just--I mean, you'd think, logically, it was in such small amounts that it's probably

not, but we're not sure.

So, I kind of hate to frighten people unnecessarily, but I think we ought to put that it's there, and that it's one-to-one with serum, which would be in the labeling. But as far as specific recommendations, I'm not sure we should make them when we have no idea what we're doing.

DR. EPPS: I agree--more information is needed. I think, in the industry information there was something about a mucosal plug. Well, we don't know whether there's mucosal absorption. Perhaps some studies could be done in that way to find out whether, you know, absorbed mucosally, because that would be an issue.

And, I guess, the issue is: the continued exposure, whether there's repeated exposure. It may not be a one-time issue. It's an issue of whether it's a cumulative effect, or whether it's a one-time effect. We just don't know. And we need more information.

DR. HOLMBOE: Just to argue for A, B and D.

MS. SHAPIRO: It sounds like we need more

information.

DR. RINGEL: One thing to take into account is that we do recommend pregnancy tests for women who are using topical tazarotene, just as a--you know, just as round number, if somebody applies one ml of tazarotene to their face, they've got about 1 mg topically. And if we're looking at semen--just quick numbers here--it looks like it's about .0001 mg in the semen, which seems awfully small.

I guess what I would do is the same thing I do in my office when I don't know what I'm talking about, I usually just tell my patients, "I really don't know what I'm talking about."

[Laughter.]

And we need to put down what we know in the package insert, and leave it to the patient's judgment.

DR. STERN: I think Dr. Ringel is absolutely correct. And going back to what Dr. Furberg--wouldn't it be nice and comforting if we had follow-up on those hundred-plus pregnancies during topical administration, where we'd have some

idea of whether there was an extraordinarily low-level effect, and that would be very reassuring to us.

And perhaps, in fact--if you'll pardon the pun--the route to go in terms of deciding whether this exposure was, in fact, one to be concerned about, since we know with the widespread topical use there are going to be a fair number of exposed pregnancies with the topical tazarotene,

DR. GARDNER: I think I would vote in favor of generating more information about these subjects, and not in favor of anything that sounds like more recommendations on things that we can't monitor or enforce.

I know you don't want to talk about the February meeting, but it does seem that we spent two days trying to understand why the contraceptive recommendations that were out there, in a known arena, may be problematic; and then to add that someone who's going to use this product for at least 52 weeks should also always use condoms seems to me to be an exercise in futility, especially on

as little data as we have.

So I would suggest that--I think someone said "A, B and D"--whatever we decided D is--but generating more information, or re-analyzing data that are there to shed light.

Also, this doesn't exist in a vacuum. We will be generating data from the risk-management programs of the retinoids as we go along anyway, and so this may appear as information we can use.

DR. WILKERSON: Well, my concern is--I mean, there's--what?--an approximately a 1 percent birth defect rate in the population? Is that right, Dr. Honein?

DR. HONEIN: About 3 percent.

DR. WILKERSON: Oh, okay. So--2 to 3. As far as I know, no one's ever died from wearing a condom, except maybe unless they had an anaphylaxis from the latex or something.

[Laughter.]

So--yeah, I don't see any problem in putting in the package labeling, that this is what's know, and the safe route is certainly to do

that.

I guess my other comment on this: I didn't see anything as far as morphologies, or sperm counts. I mean, I'm assuming, like the rest of the retinoids, this did not have an issue as far as reducing those counts, or the morphologic appearance or functioning or anything of those sperm.

VOICES: [Off mike.] [Inaudible.]

DR. WILKERSON: Oh, it's in the animal? Did I miss that one sentence?

[Laughter.]

Okay. And it did not, right?

VOICES: [Off mike.] [Inaudible.]

DR. WILKERSON: Oh, it did.

VOICES: [Off mike.] [Inaudible.]

DR. WILKERSON: It's not a big deal? Well, if you're a rat, it is.

[Laughter.]

So, yes--with cautions.

DR. DAY: A, B and D.

DR. LEVIN: A, B and D.

DR. STERN: Now we have to vote on 4.C--which we've already talked about--formally.

So why don't we just go through. And I think everyone's expressed their opinion.

Is that right? Do you need a formal vote on that particular question?

MS. TOPPER: Yes.

DR. STERN: So this question deals with--it has a lot of ambiguity, given the complexity of the question. But people can say "yes," "no" or "abstain."

"Are the scientific and clinical uncertainties surrounding--

DR. BULL: Unless there are other opinions that the committee would like to offer--

DR. STERN: Oh, great.

DR. BULL: --we are--I think you all have given us, you know, very rich input on that issue--unless there are further comments.

DR. WILKIN: Actually, several of the members mentioned "D" as one of the options. So I hope that comes back up again--5.D--when you talk

about 6; that is, what would the additional studies be?

DR. STERN: So, with being granted a buy for good behavior [laughs]--or perhaps other than good behavior [laughs]--we'll now go on to Question 6, which is, again, a discussion question. And that is:

"What additional studies are needed? Are these studies needed before or after approval of the product?"

And I think "studies" can be in the broadest sense of the word.

Who would like to start with recommendations?

DR. LEVIN: What was the result of the vote on 3? Which was approval?

[Pause.]

MS. TOPPER: There were four abstentions, three "yes" and nine "no."

DR. LEVIN: Umm--as one of the "no's" I think I want to express what I really wanted to get to was 6. I mean, the reason I voted no is because

I think that there's a lot we don't know that we need to know.

And so, two concerns: there's a lot we don't know that we need to know, and the devil's in the details of how we manage the risk of this particular product.

So, I think, in general--yes, there's a lot more. And I think we've talked about all of the missing pieces here. So I think the FDA has heard--at least as far as I'm concerned--what needs to be done.

DR. STERN: Yes.

DR. DAY: Before, one of the people on the sponsor's side wanted to tell us about the risk-management program and it wasn't an appropriate time, but we haven't heard much about it. And just having the list of all the things up there doesn't tell us.

And there are a number of things that might be in the works for the risk-management plan, to see whether--for example, Dr. Walker talked several times about the knowledge test, to prove

that the physician and the patient understand the risks and so on. And I was wondering if there was going to be comprehension testing of the messages in advance, or not.

And so there are things like this, which they already may have in their plan and so therefore I wouldn't suggest anything--but they might not. Or, they might have it in a way that would be a good way to do it, or something else might be needed.

So, in terms of general knowledge testing, we don't have enough information yet.

DR. STERN: Dr. Wilkerson?

[Pause.]

I'm just going around, since I haven't seen a lot of hands, to make sure that everyone puts in their comments about additional studies.

DR. WILKERSON: Well, probably a couple things. One, I think there is an adequate data base to approve this drug. I think there is a need in the market, and so I disagree.

You know, I think there are issues, as

there are always issues. We always need more information. But we have to draw a line.

There is a critical need in the market for a retinoid to treat certain female patients, because the alternative that we have right now is basically a bigger risk that this drug is, in terms of pregnancy. And I think to delay this approval, it is going to put a lot of people out there that need therapy in harm's way.

But, in terms of additional studies, certainly the male side of it I think is the issue, and some of these other things.

But, yes, I think sometimes we subject some of these drugs to more--far more scrutiny than what the drugs that are already on the market have been subjected to. And if we sat and picked those apart also they would not be approved if we were applying the same criteria.

DR. STERN: Dr. Gardner?

DR. GARDNER: I agree with Dr. Wilkerson. I think that we tend to talk ourselves into a lot of pre-approval requirements that may, in fact, not

be necessary or prudent.

I would like to encourage that, as the FDA develops this--there are many questions that I have about the program that I think are pending discussions on the larger retinoid thing. For example, we've talked a lot about how to make this feasible to do, and what happens with the lab tests--the lab-confirmed pregnancy tests--and some of things that we haven't heard get resolved.

I'm sure that as this develops along, working with the FDA, they will resolve them. If we could define a list of things that probably should be done sequentially with--or sorry--concurrently with approving a drug, if the dermatology community believes that it would a good addition, I think we should focus on that and see what needs to be done in order to supplement what we already have as data.

DR. STERN: I think the study that's need is one that--where the company robustly demonstrates that they've figured out a way of putting this drug into the market, that it will be

used, in fact, for its labeled indications, and not for other indications that are more--that have a prevalence of very high-risk individuals for pregnancy; and that they have--that they demonstrate that they have a way to do it, and that they have an ongoing study, in terms of really showing that that way that they're going to bring the drug to market will, in fact, be effective in having the drug used in the individuals for whom the benefit-risk ratio is likely to be the best one for a teratogen.

DR. RINGEL: One thing I'd want to make sure is--that I haven't heard quite enough of--is that this is a better drug for two-thirds of the population than is Soriatane for the indication of psoriasis. And I think that that's pretty clear.

And the problem is that it's a horrendous drug for the other third of the population, who can get pregnant. The one thing that needs to get done, as far as I'm concerned, before approval, is to solve that problem.

In terms of the other issues, I think

people are absolutely right; I mean, I'd like to see mandatory adverse event reporting for all medications, for serious adverse events. But, unfortunately, that's not the policy of this country.

I can't see singling out this particular drug. I would love to see all of these things followed up. But do I think this is worse than other things that have come out on the market? I don't think so. I really am concerned about the pregnancy issue.

MS. SHAPIRO: I guess my biggest concern at the moment is Dr. Stern's. So I would agree that if we can figure that out, that would relieve a lot of concerns.

DR. HOLMBOE: Let me just add that if it does get in the marketplace, to make sure that the outcome measures put in place from the effectiveness analysis are robust, and that it will really be approached as an observational registry study to track a number of these metrics.

DR. EPPS: I would be interested in more

information and follow-up on the fractures; for example, do people have multiple fractures, what kind of trauma is associated or not associated.

I would be interested in following up on some of the endocrine and other issues, whether they be thyroid or triglycerides. Yes, they can be treated, but if a significant number of people get them, whether it's triglyceride of 500 or 750--I mean those are high. I mean, serum looks cloudy at that point. And that's something to be followed.

Also, perhaps, more testing with the rabbits and mice, which seemed to have more data regarding this drug, when compared to the other drugs, as far as the lowest teratogenic dose. Maybe that's a good basis for a comparison--doing some trials regarding those. I guess it was in one of the--oh--I guess it's Dr. Yao's information. Those would be two animals, perhaps, where trials could be done, and maybe some comparisons there for teratogenicity.

DR. RAIMER: I think most of our concerns have been expressed. I have a little bit of a

problem that we're basically not approving a drug, in part because we're worried it could be used for something that it hasn't been presented for. I'm not sure that was our real purpose here.

So, I do have a concern that we're doing that.

DR. SCHMIDT: I, too, think that we should approve this drug, but I do think that if it is approved, that there are some studies, like the fractionating the alkaline phosphatase, the repeated checks on triglycerides--not just to not have any lab.

And then this bone thing, to follow that out more than one year, on long-term studies.

But I really think that there is a niche that we do not have a medication for, with some aspects of psoriasis, that we really do need this medication.

DR. SELLERS: I'd like to echo Dr. Stern's comments, and also mention that without some of these studies, we can't develop an adequate risk-management program. The risk assessment for

vaginal dose of the drug is critical for informing the risk-management program; also patient populations in which the drug is going to be used--and that is informed, whether we like it or not--by the off-label use.

So I think that we need to look at the effects, in these drugs, in some of the sub-populations that weren't represented in the data that was given to us.

DR. KNUDSEN: I have nothing to add. I think it's all been said.

DR. KATZ: I agree with Dr. Raimer, that we shouldn't be concerned with off-label use. After all, some of the drugs of choice in the past for certain diseases were used for years off-label; like methotrexate for psoriasis, dapsone for dermatitis hepatoformis. So that's the responsibility of the physician and the patient, who's informed, that it's off-label use.

My main concern is longer follow-up for the bony abnormalities, and the, really, efficacy--the low percentage of efficacy here. We

heard from two patients, in whom it was very efficacious. But how about the other 17 out of 20--statistically--where it wasn't equally efficacious, and they would be going through very expensive treatment that also exposes the female population to the obvious teratogenic effect.

DR. FURBERG: I abstain, because I still have a problem coming down, and interpreting the findings.

I think I would be in favor of approval for a limited indication, if we could come up with a strict management program--under that condition.

And if we do, I'd like to make it conditional upon a thorough evaluation, and a re-review in a about a year or two, to see whether the management program worked.

We have had a lot of failures along the way. But if we can set up a new, better system, and we can show, after a year or two, that it's working fine, then I'll be for opening the gates more.

And while that is underway, I wish we

could also get some additional long-term follow-up data on the patients we already have, or other ones that you may enroll; information on--as we talked about--failures; the metabolic effects on glucose, and lipids and so on.

So--but I haven't really had--I'm not getting a sense that we have come up with a strict risk-management program that would be satisfactory to me.

DR. HONEIN: Well, I think, despite the difficulties from a public health perspective, the most critical additional study to be done is to do the comparison of this drug with Accutane for acne, so that we know which one is better, and that data is available and published. And if this is as good or better, then we could develop a risk-management program with that patient population in mind. If the data is published that this is not as good, then I think off-label use would probably be minimal, and I'd have much less concern about this being approved for psoriasis.

So I think that study is the absolutely

critical additional study that I'd like the resources to be directed to.

DR. STERN: Thank you.

Dr. Wilkin, have we addressed all of the issues posed to the committee? Or are there additional questions you'd like to pose to us?

DR. WILKIN: I appreciate all the discussion. I think you went beyond the questions--

[Laughter.]

--you added additional thoughts that we hadn't even thought to ask. And so you certainly put an enormous amount of effort into reading the briefing documents, and thinking all this through.

It will take us quite a while to go back over the transcripts and digest all of this.

But we thank you very much.

DR. STERN: Thank you.

The meeting is adjourned.

[Whereupon, at 4:23 p.m., the meeting was adjourned.]

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