FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:00 a.m.

Tuesday, September 9, 2003

Holiday Inn
Montgomery Village Avenue
Gaithersburg, Maryland

ATTENDEES

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ATTENDEES (Continued)

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ATTENDEES (Continued)

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CHARLES JOHNSON, M.B., CH.B.
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JAMES KRUEGER, M.D., PH.D.
ALAN MENTER, M.D.
MARK LEBWOHL, M.D.
MICHELLE ROHRER, PH.D.
MARY STUTTS
TED WARKENTIN, M.D.

ALSO PRESENT:

LESLIE HOLSINGER
MARK LEMELIN
LYLE NEWCOMB
ROBIN PEVNICK
KADESTA PROTHRO-HARRIS

C O N T E N T S

BLA - STN 125075/0, Efalizumab (Raptiva)
by Genentech, Inc.,
to be used in the Treatment of Adult Patients
with Moderate to Severe Plaque Psoriasis

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. STERN: Good morning, everyone. I'm Robert Stern. I'm the chair of the Dermatology Advisory Committee, and this morning, we will be discussing efalizumab, also known as Raptiva, for the treatment of psoriasis.

Why don't we start by going around the table and each person introducing themselves and their role on the committee?

DR. PLOTT: My name is Todd Plott. I'm the industry representative.

DR. STERN: Could you state with whom you're affiliated?

DR. PLOTT: I'm affiliated with Medicis Pharmaceutical Company in Scottsdale, Arizona.

DR. RINGEL: I'm Eileen Ringel. I'm a dermatologist in private practice in Waterville, Maine.

DR. TAN: I'm Ming Tan. I'm a biostatistician with the University of Maryland, School of Medicine, Preventive Medicine and Epidemiology.

MS. KNUDSON: I'm Paula Knudson, the consumer representative. I'm an IRB administrator at the University of Texas Health Science Center in Houston, Texas.

DR. DRAKE: I'm Lynn Drake, and I'm on the

faculty at Harvard Medical School and I'm based at the Massachusetts General Hospital.

DR. BLAUVELT: I'm Andy Blauvelt. I'm a senior investigator in the Dermatology Branch of the National Cancer Institute at the NIH in Bethesda.

DR. MORISON: Warwick Morison, dermatologist in practice in Baltimore and Johns Hopkins University.

DR. SAWADA: Good morning. I'm Kathleen Sawada in private practice in Lakewood, Colorado.

DR. KATZ: I'm Robert Katz. I'm a dermatologist in private practice, Rockville, Maryland, and consultant in dermatology at Walter Reed Army Medical Center.

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

MS. TOPPER: I'm Kimberly Topper. I'm with FDA. I'm the executive secretary for the committee.

DR. EPPS: I'm Roselyn Epps. I'm Chief of Dermatology at Children's National Medical Center, Washington, D.C., in private practice.

DR. SCHMIDT: Good morning. I'm Jimmy Schmidt from Houston, Texas. I'm in private practice and I'm affiliated with the University of Texas and Baylor College of Medicine.

DR. PAPADOPOULOS: Good morning. I'm Elektra Papadopoulos. I'm the medical officer and clinical reviewer for the file.

DR. SIEGEL: I'm Jeffrey Siegel, Acting Branch Chief in the Division of Clinical Trials at the FDA.

DR. WALTON: Marc Walton, FDA.

DR. WEISS: Karen Weiss, FDA.

DR. MARZELLA: Lou Marzella, FDA. Good morning, everyone.

DR. STERN: Thank you very much.

Now Kimberly Topper will read the conflict of interest statements.

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests 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) and 21 U.S.C. 355(n)(4), an amendment to section 505 of the Food

and Drug Administration Modernization Act, Dr. Kathleen Sawada has been granted full waivers for ownership of stock in two competitors, one valued at less than $5,001 and one valued from $5,001 to $25,000, and for unrelated consulting for a competing company for less than $10,001 per year.

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.

We would like also to note that Dr. R. Todd Plott has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. He's Vice President of Clinical Research at Medicis Pharmaceutical Company.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a 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: Before we go on to the FDA's

presentation and reviewing these materials, I always think it's more useful to have a context to put a hearing like this in in terms of what are some of the questions and what we're really talking about. So I prepared a very brief presentation which at least gives my opinion about what the context of our task is beyond the formal part of addressing the FDA's questions.

So what we're really here today about is to evaluate a systemic therapy for psoriasis, and I think we have three tasks as advisors: one to look dispassionately at efficacy; the second to look at what the database for safety is and what are in fact the additional data we need to make a judgment about safety, how much we really do know; and the third I believe, in my experience now spanning intermittently over 20 years on FDA advisory panels, is to give the advice as clinicians and academicians about labeling that will help in the meaningful use of the drug, given what we do know today as opposed to what we hope about efficacy and safety.

So, of course, the whole reason we're here is to see if a new compound meets the needs of patients and at least a couple of us here have been treating patients with psoriasis for close to 30 years, and in my experience, what patients with psoriasis want as a therapy are an effective therapy that will clear or nearly clear them, that will

keep on working. Patients do not want to continually use a therapy, and when the disease returns, they want a treatment that will work again at least as well, and they also want something that's convenient, limited trips to the M.D., not messy, and doesn't require a lot of their time because, after all, psoriasis is a chronic disease, average age of onset about 30 or 35, which means the average individual who develops psoriasis is going to have this disease in varying severities over close to 50 years. So a 6-month fix or a 1-year fix really means relatively little in the time.

What else they want, of course, is safety and from a patient's perspective, safety means two things. One is acute safety, that is, it doesn't make them uncomfortable when they're using it; and the second is long-term safety and part of long-term safety is does use of the medication in fact preclude or interact with either future or prior treatments, increasing the risk in those groups, because again we're talking about people using multiple therapies over many decades.

As I mentioned, it's a chronic disease. It's extent and impact vary greatly among patients, and in the given individual over time, there's a reasonable amount of data that suggests if you take two individuals who are demographically exactly the same, whose disease is the

same, and one who's 25 and one who's 75, on average, the 25-year-old will find that the disease has a greater impact on them. So one has to consider not just how much there is, not just where it is, but what it means to the particular patient.

So the questions for today with efalizumab is: does it work, does it keep on working, is it safe, and do its potential benefits outweigh its risks? And in addressing the issue, I would hope -- at least I approach the issue in reading the materials put forward both by the FDA and the sponsor -- to look at what evidence we have for it working, for efficacy, and that is, in what types of patients has efficacy been demonstrated, how well and often does it work? Remember that statistically significant is not enough if a drug has any risks and therefore magnitude of benefit is important.

And what are the factors associated with success or failure, and one reason for this is in deciding on labeling or advice is if there are available data that help us select patients who are more likely to both tolerate and respond to the drug, clearly we want to know that from the available data, and if those are key points, perhaps we want to make recommendations about the kinds of studies that would better define the susceptible groups.

Because psoriasis is a chronic disease, my own

opinion is anything that works for just a little bit is really not much of an addition to our therapeutic armamentarium. So we want to know does it keep on working, and if a treatment has risks, clearly we want to know what it does in terms of the natural history. Do people after they come off therapy rebound, how long do they stay clear off of therapy, and what do patients really think about its efficacy, both absolutely and relative to therapeutic options?

I understand absolutely that in today's hearing we are not comparing drugs, but when we think about benefit to patients, we must always think does this really add anything to what patients are doing, not a regulatory decision but speaking as a clinician and not head of this panel.

Is it safe? Short-term safety, we will hear a fair amount about, and again long-term study with repeated use for a drug that does not, in fact, cure a disease and must be used repeatedly if it's to have any long-term impact, we have to know what's the long-term safety.

My own concerns for this class are infection, cancer, especially lymphoma and squamous cell carcinoma of the skin, immunologically-mediated diseases that have been described with certain other agents in this general class, as well as immunologic reactions to the drug, that is, the

development of antibodies, particularly in a product that is not a pure human antibody, and that's both because it may decrease efficacy and perhaps that antibody antigen reaction may, in fact, have independent health risks.

So my question today, and I hope everyone's question, will be, do we have sufficient and robust data to really make strong statements both about short- and long-term efficacy? I have another question, very unpopular with the FDA, which is it likely that post-marketing surveillance will, in fact, provide timely and robust data, that is, can we rely on phase IV commitments?

I'm sure many people in this room are aware of the study that showed that less than 40 percent of phase IV commitments were fulfilled, even in a technical sense, and so the question is, can we really rely on phase IV commitments and what assurances will we have that those will be carried out?

So do the benefits outweigh the risks, which is, after all, always the question. My own opinion is that the short-term perspective is insufficient. A long-term view is needed. We have to look and see whether available data allow us to recommend approval and what labeling will put the drug in proper perspective, given what we know today.

So I'd like to make a proposal, not being at

the Alefacept meeting but having read good parts of the transcript, to try to focus on us a little bit today. Acknowledging the limitations of the evaluation metrics utilized in psoriasis, let us agree that those utilized and agreed upon between the sponsors and the FDA as the two main endpoints -- not primary endpoints, there can only be one -- be the ones we talk about today. Let us not get into digressions. Let's talk about in terms of efficacy. PASI 75 and clear or almost clear, and let's not try to complicate the discussion of this product with debate about other criteria and how to measure improvement in psoriasis. I feel that those things will just end up being a digression and take us away from the important issues of the day.

I also think it's important because, as I mentioned earlier, assuming we recommend that it is approvable, some of what we can do is advise the FDA about what context in terms of what labeling might be helpful to particularly the learned intermediary, i.e., the prescribing physician, in using this drug as opposed to other drugs, one of the main purposes of labeling. So I think in doing that, it's interesting and important to look at what current labeling is for other drugs, from systemic drugs for moderate to severe psoriasis.

Here's one that a few of us have had some

involvement with over the years. We call it PUVA but it's methoxsalen, and this is the labeling in terms of the indication. I won't get into safety. Methoxsalen is a potent drug. Photochemotherapy, methoxsalen with long-wave UVA radiation, is indicated for the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.

Soriatane, an aromatic retinoid, is indicated for the treatment of severe psoriasis. Because of significant adverse effects associated with its use, Soriatane should only be prescribed only by physicians knowledgeable in the systemic use of retinoids.

I'm sorry. There should be another slide. Methotrexate is indicated for the symptomatic control of severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy but only when the diagnosis has been established as a biopsy and/or after dermatologic consultation.

Neoral, psoriasis. Neoral is indicated for the treatment of adult non-immunocompromised patients with severe -- i.e., extensive and/or disabling -- recalcitrant plaque psoriasis who have failed to respond to at least one systemic therapy.

Amevive is indicated for the treatment of adult

patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

So, again, coming back to today's task, we're here to answer the FDA's questions. We're here to judge if in fact, based on available data, benefits outweigh risks, and I think we're also here to suggest additional data for judging the long-term role of this product and in aiding in both current and perhaps altered labeling, should it be approved.

Thank you very much.

Dr. Kozlowski will now present an introduction to the candidate product.

DR. KOZLOWSKI: I'd like to thank the chair and the members of this committee and to welcome all the participants to this meeting to discuss efalizumab for the treatment of psoriasis.

I'd briefly like to show that a number of individuals who are not presenting here from the FDA were involved in the review of this license and contributed greatly to this.

Basically, I'd like to start by talking about the name. Efalizumab is the USAN name and Raptiva is the proposed trade name for this product. During development, there were a number of other names used for this antibody.

The product is a humanized IgG1 kappa

monoclonal antibody and its target is the CD11a chain of LFA-1.

The proposed indication for this is treatment of moderate to severe plaque psoriasis in adults, and the rationale for this is that lymphocyte-derived cytokines or other growth factors or mediators can lead to keratinocyte hyperproliferation. Down-modulation, both of lymphocyte number and their state of activation in the skin, should potentially reduce these cytokines or mediators. LFA-1 is an important molecule in lymphocyte adhesion, activation, and migration to tissues.

To talk a little bit about the structure of LFA-1, it's composed of two chains. It has CD18, which is shared with a number of other white blood cell-based integrins involved in adhesion, and CD11a, which tends to be more specific for lymphocyte interactions.

There are a number of ligands for this. In fact, for this family of molecules, there are diverse ligands, including parts of complement, but the primary ligands involved are the intercellular adhesion molecules.

ICAM-3 is one involved in early T cell activation. ICAM-2 is one that's constitutively present in endothelium and other cells, but ICAM-1 is the one that tends to be induced by inflammation and would be likely to play the most important role in a chronic inflammatory

disease.

So this interaction between LFA-1 and ICAM-1 is dependent on a domain of the LFA-1 molecule called the I domain which has a number of epitopes that have been recognized by monoclonal antibodies, and efalizumab interacts with one of these epitopes on the I domain, thus interfering with the interaction of ICAM-1 and LFA-1 and preventing this adhesive interaction.

But how does this adhesive interaction relate to lymphokine function in a disease process? So first, I'd like to talk about the role of LFA-1 in adhesion and co-stimulation of T-lymphocytes.

Any interaction with lymphocytes tends to begin with antigen. I mean there are super-antigens and other things that can drive T cells, but there's usually an antigen. In the case of psoriasis, it's not so clear what the antigen is. People have talked about streptococcal antigens, but in any case, there needs to be some driving force to activate this process of lymphocyte release of cytokines.

Antigen doesn't work alone on T cells. It needs to be presented in the context of a major histocompatibility complex molecule, generally on a cell which is presenting antigen. This complex is then recognized by the T cell receptor and, through a series of

signal transduction molecules associated with it, begins the process of activating T cells. This can happen in conjunction with co-receptors, such as CD4 and CD8, and leads to what's referred to as signal 1.

Now, although this is the antigen-specific part of the T cell activation, it's not enough to really drive full T cell activation, and there are other molecules. The most-classically defined pair is B7 and CD28 which provide a second signal that allows full lymphocyte activation. There are other molecules which contribute to this in adhesion, such as LFA-3 and CD2. This is a pair that's involved in Alefacept, another therapy for psoriasis.

For this signal 1 and signal 2 to work together, recently it's turned out they not only need to interact, but they need to interact in a particular geometry, which is referred to as the immunologic synapse, and when they interact, they produce cytokines, such as IL-2, interferon, IL-8, and may produce other growth factors in some way or another that lead both to proliferation of T cells and signals to keratinocytes to proliferate.

But for all this to happen and this synapse to form, one needs the cells to come togethe,r and LFA-1/ICAM-1 play a role in allowing the cells to adhere for the APC to meet the T cell to begin with, and it also plays a role

in forming the geometry of the synapse, forcing the other molecules together in a localized patch that can allow the activation to occur.

So in addition to these two functions of forming this geometry and making the cells contact, LFA-1 can also transmit a second signal of its own, and in fact, there's some data that suggests that this second signal is more important in CD8 T cell activation than CD4 and there's some evidence that in psoriasis CD8 T cells are increased over CD4 at the site of lesions and may play an important role in some forms of psoriasis. So clearly interfering with this interaction interferes with lymphocyte activation in a broad range of ways.

However, in addition to this phenomenon of T cell activation, which can occur both in secondary lymphoid organs, like lymph nodes or spleen, but also can occur at the site of inflammation itself in the skin, the question of how lymphocytes actually get to the skin or the target tissue is another avenue in which antagonists of LFA-1 can play a role.

So if the top of this slide represents the blood vessel and the bottom represents the target tissue and there's a lymphocyte in the bloodstream, the lymphocyte has cell surface molecules integrins, such as LFA-1 which we just described. It also has chemokine receptors and it

also has a family of selectins which, through carbohydrate interactions, form adhesive interactions.

In order for a T cell to get where it's going, first selectins generally interact with the endothelium and this causes the cell to slow down and kind of roll along the blood vessel. Then chemokines, which are secreted or which are present in the matrix of the endothelium, can then interact with chemokine receptors on the lymphocytes which causes them to increase the evidity of LFA-1, so that it strongly binds ICAMs on the endothelium, and this leads to cell adhesion and spreading.

Finally, integrins can play a role in tethering the forces that allow the lymphocyte to transmigrate through the endothelium into the tissue, and again once the lymphocyte is in the tissue, it can interact with the antigen-presenting cells in the skin or with keratinocytes through the mechanisms shown in the previous slide. So there is a wide variety of ways in which LFA-1 can interfere with lymphocyte activity at the site of psoriasis.

But this mechanism tells us something about the general things to think about for this product. This broad range of activities is directed against all leukocytes, not just ones that are specific for psoriasis, and thus this is an immunosuppressant, and this was considered and should be

discussed in terms of the clinical studies involving the safety of this product and makes us think also about issues in terms of its effects on immunizations and also think about issues in terms of its potential effect on a developing thymus, if it's exposed in that way.

I'd like to talk a little bit about the development of this product. This was initially developed as a monoclonal antibody in a mouse and thus was a murine product. Since this is a product which is going to be used chronically because of the disease state, it's important to try and reduce immunogenicity to all extents possible, and one strategy to do this, which is to reduce and not eliminate immunogenicity, is to make the antibody as human-like as possible and there are a number of strategies to do that.

The most important region in the antibody for binding are the variable regions, which are actually shown in red in the chimeric antibody, and so one strategy of making an antibody less immunogenetic is to leave the variable regions which bind as murine and the constant regions can then be human.

But there's a sort of even more advanced strategy, although whether it actually reduces immunogenicity further is not so clear but in theory it could, and that is to just have the complementarity-

determining regions, which are the very sequences that determine binding, to be the ones from the murine antibody and everything else human. And a strategy of that nature was used in generating efalizumab to reduce the possibility of immunogenicity, although again it doesn't eliminate it.

I want to talk a little bit about the manufacturing scheme for the antibody. The antibody is made in Chinese hamster ovary cell lines transfected with vectors that contain the genes for the efalizumab heavy and light chain, and this is a system that's been used for a number of products. The host cells are grown in serum-free medium. There's every attempt to minimize animal-derived materials. The purification process has multiple steps and is designed to try and remove contaminants throughout the process. A strategy in this product was made for concentration lyophilization in order to allow the antibody to be in a small volume and facilitate subcutaneous administration.

I also want to talk briefly about the manufacturing development of the product. The product was initially manufactured by Xoma and then later by Genentech. Although the manufacturing process had some change on pharmacokinetics, it did not have any change on the pharmacodynamics of the product. Both products had similar clinical and efficacy data, as will be discussed in the

clinical section, and therefore we are considering that the data that is shown from both the old material and the new material can be pooled in support of the to-be-marketed Genentech product.

Finally, just a comment. This is a robust manufacturing process. However, we're still in the process of the license and a number of manufacturing control issues are still under discussion.

Thank you very much.

DR. STERN: Thank you.

We'll now move on to the Genentech presentation. Dr. Michelle Rohrer will begin.

DR. ROHRER: Dr. Stern, advisory committee members, FDA, and guests, good morning. My name is Michelle Rohrer, and I am Director of Regulatory Affairs at Genentech.

At Genentech, our research is focused on the development of targeted therapies to treat unmet medical conditions, and we are pleased to be here today to share our data on Raptiva, a targeted therapy that we have developed in collaboration with Xoma to treat patients with moderate to severe plaque psoriasis.

Our agenda this morning is outlined on this slide. Following my brief introductory remarks, Dr. Mark Lebwohl of the Mount Sinai School of Medicine will give you

a review of plaque psoriasis and the unmet medical need. Then Dr. Charles Johnson of Genentech will summarize Raptiva's mechanism of action and detail the rationale for the selection of doses used in the clinical program. Next, Dr. Lee Kaiser will summarize Raptiva's efficacy profile, followed by Dr. Richard Chin who will give you an overview of Raptiva's safety profile, and to conclude our presentations, Dr. Charlie Johnson will return with an overview of Raptiva's benefit-risk profile.

I'd just like to note that for you all, you each have copies of these presentations in front of you and you're welcome to follow along as we move through the presentation.

Now, we also have with us several expert clinicians. I've already introduced Dr. Mark Lebwohl. He's Chairman and Professor of the Department of Dermatology at the Mount Sinai School of Medicine. Dr. Alan Menter is here as well and Dr. Menter is Chairman of the Division of Dermatology at Baylor University Medical Center in Dallas. In addition, Dr. James Krueger is here and Dr. Krueger is a Professor of Dermatology at the Rockefeller University.

It's important for you all to know on the committee that Drs. Lebwohl, Krueger and Menter participated in the Raptiva Program as clinical

investigators and as such, they have treated large numbers of patients with Raptiva. We hope that you'll find their experience valuable.

Dr. Ted Warkentin is here as well and Dr. Warkentin is Professor of Medicine and Pathology at McMaster University. Dr. Warkentin is a hematologist with a specialty in platelets, and we hope that you will use his expertise as you consider the question before you regarding platelets.

Shown on this slide is the indication that we're seeking today. Raptiva is indicated for the treatment of adult patients, 18 years or older, with moderate to severe plaque psoriasis.

Raptiva is a recombinant humanized monoclonal antibody. It is provided as a lyophilized sterile powder in a 2-cc vial. It is reconstituted with sterile water for injection to a final concentration of 100 milligrams per ml. We recommend dosing once a week with a 1 milligram per kilogram subcutaneous injection.

Genentech and Xoma have performed 13 psoriasis clinical trials and we have treated 2,762 psoriasis patients with Raptiva. Four of these clinical studies were double-blind placebo-controlled phase III trials and those trials are highlighted at the top of this slide. In addition, we currently have long-term treatment trials

ongoing.

These trials taught us how to best use Raptiva. When the program began, we did not know whether Raptiva would be best used intermittently or continuously, and during the course of these trials, it became clear that Raptiva is really best used continuously.

In our presentations, we will share that Raptiva is effective and safe. In clinical trials, Raptiva improved plaque psoriasis across every endpoint. Importantly, it improved patients' quality of life and alleviated their psoriasis symptoms. In these clinical studies, Raptiva was well tolerated and safe for continuous use.

Regarding studies in pediatric patients, for the BLA, we requested a waiver from studying infants and children through the age of 12. We do not feel that it would be appropriate to expose still-developing immune systems to Raptiva which is an immunosuppressant. With regard to studies in adolescents whose immune system is still maturing, we have requested that these studies be deferred until more safety data is available in adults.

We recognize that large numbers of patients will need to be treated for long periods of time in order to best understand Raptiva's safety profile, and we are fully committed to a large phase IV safety surveillance

study in order to further characterize Raptiva's safety profile.

And now it is my pleasure to introduce Dr. Mark Lebwohl.

DR. LEBWOHL: Thank you very much. Dr. Rohrer has already told you that I've been intimately involved in the efalizumab clinical trials. Even though I'm chairman of the Department of Dermatology at Mount Sinai, I spend a large proportion of my time seeing patients and there is virtually not a day where I don't see a patient with psoriasis this severe in my practice. You can imagine the impact that this degree of psoriasis has on the life of the patient that you see here. He has obviously a large percentage of his body surface area affected, but even patients who have lesser degrees of surface area involved can have the disease create a major impact on their quality of life.

In particular, when psoriasis involves the hands and feet, even though the percentage body surface area affected may only be 3 or 4 percent, this interferes with every aspect of things that we take for granted, every aspect of life, for example, buttoning your shirt or shaking hands if it involves the palms, if it involves the soles, pain on every step that they take. So even though the body surface area may be small, the impact on quality

of life is major.

It is estimated that approximately 4.5 million American adults have psoriasis and approximately 10 percent of those have moderate to severe disease, so about half a million patients are candidates for systemic therapy. The patients who have moderate to severe disease understandably have a major impact on their quality of life, yet it has been shown that the majority of them are not using the most aggressive treatments for their disease.

The Short Form 36 is a health survey tool that allows us to compare the impact that different diseases have on the lives of patients with particular emphasis on physical components, on physical function, and separately on mental components. This was performed and psoriasis was compared to other diseases. Low scores are worse, and as you can see here, in terms of physical functioning, psoriasis scores more poorly than cancer, depression, hypertension, arthritis, myocardial infarction, and diabetes. Only congestive heart failure scored more poorly than psoriasis using that tool.

Looking at mental components of the disease, psoriasis scored more poorly than myocardial infarction, hypertension, diabetes, congestive heart failure, cancer and arthritis, and only depression scored more poorly than psoriasis using that tool. Part of the reason that

patients score poorly on that is the frustration they have with treatments and that was shown in a survey published in 2001. 78 percent were frustrated with treatment, 32 percent, or nearly a third, felt that the treatment they were given wasn't aggressive enough.

We have excellent treatments for psoriasis. UVB phototherapy has been around since the 1920s, has a long track record of safety and efficacy, and I generally do not encourage patients who are satisfied coming three times a week for UVB phototherapy to switch their therapy because it is a safe treatment that's been around a long time. But patients who end up coming once a week because they can't make it in three times a week and therefore don't have their psoriasis respond or patients who don't respond to sunlight and are not likely to respond to UVB phototherapy are patients for whom I would be looking for another treatment.

It's the frequency of the visits that patients complain about more than anything else, even if the phototherapy unit is right next door to them. Taking that time out three times a week at least to go and get the phototherapy is a issue.

PUVA has many of the same drawbacks as UVB. It requires two or three treatments a week for at least several months out of a year, but in addition, there are

concerns about skin cancer. Very clearly, squamous cell carcinoma is increased and more recently it's been shown that there's an increased risk of malignant melanoma as well.

Acitretin. One main drawback for women of childbearing potential is its teratogenicity, but as monotherapy, it is simply not a very satisfying treatment. However, when used in combination with phototherapy, it ends up being quite effective and that is the main way in which certainly I use it.

Methotrexate is a dramatically-effective therapy for psoriasis but has the drawbacks of bone marrow toxicity. Even though dermatologists are very good at prescribing methotrexate and think we can prescribe it safely -- and I believe we can -- patients end up seeing other doctors and then the other doctor puts them on a different drug and even though we've told the patients if you take any new drug, you have to ask my permission, I can't tell you how often patients will call in and say, oh, by the way, I was put on this antibiotic or this nonsteroidal anti-inflammatory drug last week, I hope it's okay, and yes, I took my methotrexate. It is because of that that certainly every year, and probably every month, there are cases of neutropenia and death from methotrexate.

Hepatotoxicity is a recognized long-term side

effect of methotrexate. Hepatic fibrosis occurs and as a result the guidelines currently available in the United States call for periodic liver biopsies in patients treated with methotrexate.

Cyclosporine is nephrotoxic essentially in 100 percent of patients if you give enough of the drug for a long enough period of time and because of that, our guidelines have called for limiting use of cyclosporine to one year.

Alefacept, which is the most recent addition to our armamentarium against psoriasis, has avoided many of the side effects, such as nephrotoxicity and hepatotoxicity, but it does still require weekly office visits for IM or IV administration and has a slow onset of response. Often patients don't even begin to respond until they're receiving the drug for at least a couple of months.

Because of the side effects of psoriasis therapies, the concept of rotational therapy has evolved, and the reason for this concept is that we avoid the cumulative toxicities of each of the drugs. So patients might be treated with cyclosporine for a period of time, then move to methotrexate for a period of time, then move to another form of therapy. But it is because of our concern about the side effects that that whole concept has emerged.

As a practicing clinician, I have several concerns about the treatments we use for psoriasis. I mentioned the safety concerns we have. The needs that we have: our need for safe, convenient, and effective treatment that reduces psoriasis; need for a treatment that is safe enough to give long-term; and need for a treatment that is rapid-acting.

I'd like to spend just a minute or two describing the tool that has been used in the clinical trials with efalizumab which is the PASI score because I believe certainly nondermatologists don't understand this and even many dermatologists don't understand this tool. If you asked me what proportion of patients I treat with methotrexate are cleared, I would say the vast majority. I'd say 80 or 90 percent.

This is a slide that I got from Jerry Krueger who, together with his fellow Dr. Callis, presented this work at the SID in 2002. This was a group of patients treated with methotrexate between 15 and 30 milligrams per week. They started at 15 and over 6 months went up to 30 to the maximum tolerated dose or the effective dose. What they found in looking at PASI scores is that 65 percent of patients achieved a PASI 50, 26 percent achieved a PASI 75, and 90 percent, improvement in PASI score.

The PASI score does not translate into percent

improvement of psoriasis. Many of us misunderstand the PASI 75 as meaning a 75 percent improvement in psoriasis and that clearly isn't the case. If you ask patients the degree of benefits they get from achieving a PASI 50, many of them are very satisfied with the PASI 50, in fact delighted with the PASI 50. I'll show you an example of that in a minute. So the PASI 50 is misunderstood as being a percent improvement in psoriasis and that's not what it means.

Now, just to give you an example of that, this is a patient at baseline who has a PASI score of 18 and, after completing 12 weeks of efalizumab has, a PASI 6.8. Now, you can imagine how delighted this patient was, and Dr. Stern, in your presentation, you said patients want to be clear or almost clear. If you ask this patient, he'll say I'm clear, but he doesn't achieve a PASI 75 and that is the flaw in the tool. So this patient was technically a treatment failure in the trial that was done.

So, to summarize, psoriasis a chronic, lifelong disease that causes significant disability. Its current treatments have limitations and there's a need for a safe and effective treatment for long-term use.

And with that, I'll turn the podium over to Charles Johnson.

DR. JOHNSON: Thank you, Dr. Lebwohl. My name

is Charles Johnson. I'm a Senior Director at Genentech and I am the head of the Clinical Development Group for Specialty Biotherapeutics.

My task is to discuss briefly before you the mechanism of action of this drug and then go on to how we established the dose we would take forward into the clinic. I'd like to take this opportunity to thank Dr. Kozlowski for a very thorough and eloquent review of the mechanism of action which makes my job much easier.

So as he described, efalizumab is a humanized monoclonal antibody, and it uses the backbone or the structure that we at Genentech have used for a number of our humanized monoclonal antibodies. We use the same mechanism with all of these molecules in that we use the IgG1 kappa consensus sequence into which we insert by site-directed mutagenesis the complementarity-determining region which has been raised in a mouse against the specific antigen or protein that we're targeting.

In this case, it is the CD11a subunit of the leukocyte function antigen number 1, and Dr. Kozlowski has described its activity or its action in some detail, and I'll just briefly review that in the context of the importance of establishing the immunological synapse so that there can be appropriate presentation of the antigen peptide by the MHC to the T cell receptor by the antigen-

presenting cells shown here in diagrammatic form to the T cell, which is then subsequently activated. As he mentioned, when you establish this nice contact between these two cells, it enables the facilitative presentation of this antigen by using these co-stimulatory molecules. Disruption of this by binding with another antibody which disrupts that interaction will therefore presumably produce down-regulation of this activation and the cytokines which are so important in this disease.

So, therefore, LFA-1/ICAM interactions are important both for activation of T cells by antigen-presenting cells, for trafficking of the T cells to the dermis, and also for the interaction between those activated T cells and the keratinocytes.

LFA-1 is a predominant integrin expressed on T cells, and whilst it is, in fact, expressed on other leukocytes, it is not the predominant integrin which is expressed. It's the predominant beta 2 integrin which is expressed on those cells, and so their function is relatively preserved in terms of the alternate integrins which they express.

This next slide shows a series of histological samples taken from a patient of Dr. Krueger's which shows the potential activity of the molecule. Just to walk you through it, on the left-hand panel, you see three different

stains of the same section of pretreatment, nonlesional skin taken from the patient. So you will see this is normal skin. Hematoxylin eosin stain is a stain which stains for T cells and a stain which stains proliferating keratinocytes.

Prior to treatment, you could see that this patient had the typical pattern of plaque psoriasis with thickened epidermis, a large influx of T cells into that region, and the proliferation of keratinocytes throughout that epidermal layer. After 8 weeks of treatment with efalizumab, you see marked shrinking of the epidermal layer with almost complete restoration of the integrity of the stratum corneum, a reduction relatively in the number of T cells that are there and also a restoration of that normal pattern of proliferating keratinocytes to the basal layer of the epidermis. So this suggested then that the molecule had significant potential to be an effective therapy.

So we now turned our attention to how much drug do we need to give. So we know that efalizumab binds to CD11a on the leukocytes, and as well as its saturating that binding, it in fact down-regulates and down-modulates the expression of CD11, particularly on the T cell receptors. So they are about 85 percent down-regulated. This saturation and down-modulation is rapidly effected and it's seen both after intravenous and subcutaneous doses after

about 24 to 48 hours. The full effect of that PD is maintained when we dose at weekly intervals.

So this describes in some detail both the pharmacokinetics, the amount of drug in the serum, and the pharmacodynamics, the expression or blocking of that CD11a. So here we have an experiment where we have dosed individuals at weekly intervals represented by those white arrows for a period of 12 weeks. We then follow them out to see what happens.

In the yellow line, you see the elevation of drug in the serum which is maintained as long as we continue to dose these patients, with rapid washout of the drug over a period of 4 to 8 weeks.

If we turn our attention to the blue-shaded curve, you will see this represents the number of unbound CD11as which are available potentially for binding and effectively they are completely down-regulated to the level that we can detect them and that level is maintained, completely blocked in other words, for the period that we continue dosing. When we stop dosing, there's rapid return of those CD11a unbound sites to nearly the normal baseline level. So the effect of the drug is rapidly reversible.

The dose that we used was originally in the intravenous dosing and we found that .6 milligram per kilogram intravenously would maximally down-regulate and

block those CD11a receptors. When we dosed the drug subcutaneously, we found that it was about 50 percent bioavailable. So we, therefore, hypothesized that an effective dose in the clinic would be somewhere between 1 and 2 milligrams to product that maximal down-regulation of CD11a.

We tested both 1 and 2 milligrams in the clinic, and we found that our assumption was correct, that it was maximally blocked, and we also found, as Dr. Kaiser will show you in the next series of slides, that there was no significant advantage in terms of efficacy of the 2 milligram dose over the 1 milligram dose.

So in summary then, this is a monoclonal antibody with selective immunosuppressive effect which is targeted to the CD11a subunit of LFA-1. It inhibits T cell activation and trafficking, and when we dose it subcutaneously at a dose of 1 milligram per kilogram per week, we effectively block completely CD11a T cell function. This effect is reversible.

I'll now turn the podium over to Dr. Lee Kaiser who will review for you the efficacy of this molecule.

Thank you.

DR. KAISER: Good morning, ladies and gentlemen. My name is Lee Kaiser, and I'm Director of Clinical Biostatistics at Genentech. We believe that

Raptiva is highly effective and provides significant benefit to psoriasis patients. I'll present the results of our phase III studies and show how we came to this conclusion.

We have four randomized, double-blind, placebo-controlled phase III studies of Raptiva in psoriasis patients. Per agreement with the FDA, study 2390 serves as our pivotal study. Studies 2600, 2058 and 2059 provide supportive evidence of efficacy. As our pivotal study, study 2390 forms the basis of much of my presentation.

We have the following conclusions about the efficacy of Raptiva. Raptiva has significant efficacy after 12 weeks of treatment. Raptiva has an early onset of efficacy with efficacy demonstrated 4 weeks after the start of treatment. When Raptiva is stopped, psoriasis returns. Raptiva is effective on retreatment, and finally, the efficacy of Raptiva improves with continuous treatment past 12 weeks.

This slide serves as a road map to my presentation. I'll start with our first conclusion and begin with the design of study 2390.

Eligible patients had plaque psoriasis for at least 6 months. They had a psoriatic body surface area of at least 10 percent and a Psoriasis Area and Severity Index of at least 12. Patients were candidates for or had a

history of systemic psoriasis therapy. These criteria are well recognized as defining a population of patients with moderate to severe disease.

During the screening period, patients were washed off of psoriasis medications, making this a study of Raptiva monotherapy. At day 0, patients were randomized to double-blinded study medication, either placebo or Raptiva, 1 milligram per kilogram per week for 12 weeks. Efficacy variables were collected at baseline throughout the treatment period and at week 12, which was our primary analysis time point and which was 1 week after the last dose of Raptiva.

Our primary efficacy variable was the Psoriasis Area and Severity Index. The PASI is the physician's assessment of the extent of psoriasis and the degree of plaque erythema, thickness, and scaling. The index ranges from 0 to 72, with higher scores worse.

Our primary analysis of the PASI was the rate of PASI 75 response. A PASI 75 responder is a patient with a PASI percent improvement from baseline of at least 75 percent, and a PASI 75 non-responder has an improvement of less than 75 percent. The PASI is widely used in psoriasis clinical trials, and an analysis based on a PASI 75 response represents a high bar for the demonstration of efficacy.

We assessed a broad array of secondary efficacy variables. We analyzed the PASI 50 which is defined analogously to the PASI 75 but is based on a cutoff of a 50 percent improvement. We also analyzed the PASI percent improvement from baseline as a continuous variable. We had two physician's global assessments. The results of the analyses are presented in the briefing book and are completely consistent with the results of our primary PASI 75 analysis.

We collected numerous patient-reported assessments. I'll focus on our quality of life assessment, the validated Dermatology Life Quality Index. The DLQI assesses the extent of problems patients have with symptoms, well-being and activities of daily living. The index consists of 10 individual items, each rated by the patient as not at all, a little, a lot, very much or not relevant. The overall DLQI score is the sum across these 10 items and ranges from 0 to 30, with higher scores worse. Results for our other patient-reported assessments are reported in the briefing book and all consistently demonstrate the efficacy of Raptiva.

Patients in our pivotal study 2390 had a mean age of 45. Approximately two-thirds were male and 90 percent were white, largely consistent with the overall demographics of psoriasis patients, although we enrolled

somewhat more males than females.

Patients had longstanding disease, approximately 60 percent had a history of systemic therapy, and baseline PASI and baseline psoriatic body surface area were consistent with the diagnosis of moderate to severe disease.

This chart contains the results of our primary efficacy analysis, the rate of PASI 75 response at week 12. The placebo response rate was very low at only 4 percent, and the Raptiva rate was significantly higher at 27 percent, almost 7 times the placebo rate.

Now, one detail of the analysis, there was a low 6-percent dropout rate in each treatment group; however, dropouts were considered to be non-responders. So this is a rigorous intent-to-treat analysis of efficacy and Raptiva displays clear benefit.

To illustrate the clinical significance of PASI responses, I'll show some before and after photographs of Raptiva-treated patients. Here's an example of a PASI 75 responder. This patient had a 95 percent improvement in PASI and had excellent clearing of his disease. Here's an example of a PASI 50 responder. This patient had a 67 percent improvement in PASI and had a dramatic response to Raptiva treatment. So we feel that PASI 50 represents clinically-meaningful patient benefit, and this chart

presents the rates of PASI 50 response at week 12. The placebo rate was low at 14 percent and the Raptiva rate was dramatically higher at 59 percent, more than 4 times the placebo rate.

Here are the results of our quality of life assessment, the Dermatology Life Quality Index. This chart shows the mean DLQI improvement from baseline at week 12 and mean baseline DLQI itself was just below 12 in each treatment group. The placebo-treated patients improved little and the Raptiva-treated patients improved significantly more. The value of 5.6 represents an improvement of almost 50 percent of the mean baseline level.

Now, it can be difficult to appreciate the clinical significance of this quality of life benefit and this chart helps in that interpretation. It shows the percent of patients reporting problems rated as a lot or very much, at baseline and at week 12, for each of the individual DLQI items and to explain the chart, I'll focus on the individual item of symptoms which comprises itching, pain, soreness, and stinging.

At baseline, just over 70 percent of patients reported significant problems with symptoms, rating those problems as a lot or very much. After 12 weeks of Raptiva treatment, the percent of patients reporting significant

problems with symptoms was 25 percent, for a two-thirds reduction from the baseline level. As you look across the other nine DLQI items, you see a similar pattern with rates at 12 weeks representing a reduction of one-half to two-thirds from the baseline level, indicating a substantial quality of life benefit with Raptiva treatment.

I'll now introduce the PASI results in our supportive studies, 2600, 2058 and 2059. Now, importantly, the entrance criteria and design of these supportive studies were entirely consistent or were nearly identical, rather, to the entrance criteria and design of our pivotal study 2390.

So the results in 2390 you've seen before, and across the supportive studies, Raptiva was significantly better than placebo in each study and the results in the supportive studies are entirely consistent with those in study 2390.

Now, studies 2058 and 2059 also included a 2 milligram per kilogram group and I'll overlay those results on this chart.

The PASI 75 response rate at 2 milligrams per kilogram are approximately 28 percent and right in line with the results at 1 milligram per kilogram, indicating no further benefit of 2 over 1 milligram per kilogram.

This is the identical chart for PASI 50 at week

12 and I want to make two points. Across the supportive studies, Raptiva is significantly better than placebo in each study with results entirely consistent with those in study 2390, and second, it's clear that there's no further benefit of 2 over 1 milligram per kilogram.

To this point, we've seen that Raptiva has significant and clinically-meaningful efficacy after 12 weeks of treatment. I'll move now to the onset of efficacy.

This graph shows the mean PASI percent improvement versus study week. Raptiva is significantly better than placebo at the week 4 visit and at all subsequent visits. Further, the difference between the Raptiva and placebo means increases with each subsequent visit throughout the treatment period.

This is a similar graph for the Dermatology Life Quality Index and it shows the mean DLQI improvement versus study visit. Again, Raptiva is significantly better than placebo at the week 4 visit and at the subsequent visits, and further, for the Raptiva-treated patients, the mean improvement at week 4 is fully 70 percent of the mean improvement at week 12, indicating a substantial early quality of life benefit with Raptiva treatment.

In addition to the demonstration of the efficacy of 12 weeks of Raptiva treatment, our phase III

studies were designed to evaluate extended treatment with Raptiva. Regarding intermittent treatment, we evaluated how efficacy is lost when Raptiva is stopped and how patients respond to retreatment. Study 2058 had study periods that addressed these two issues.

I previously presented the PASI results in the first 12 week treatment period of study 2058. Raptiva-treated patients who were PASI 75 responders at week 12 were entered into an observation period, and in order to evaluate the durability of response, patients were given no further Raptiva treatment or other psoriasis therapies. Patients were then observed for relapse which was defined as the loss of at least half of a patient's PASI improvement at week 12 of the treatment period. Upon relapse, patients were randomized to 12 weeks of double-blind placebo or Raptiva.

There were 107 patients who started the observation period and this chart shows the proportion of patients who have relapsed versus weeks since the last dose of Raptiva, and consistent with the reversible effect of Raptiva on CD11a expression, the median time to relapse is just over 2 months. Importantly, there's a qualitative aspect of relapse that is not apparent on this slide. Some patients experience psoriasis adverse events upon Raptiva discontinuation and this will be described by Dr. Chin in

his summary of safety.

Now, recall that once patients relapsed, they were randomized to 12 weeks of double-blind placebo or Raptiva, and this chart shows the PASI response rates in this retreatment period. Now, clearly Raptiva is effective in the retreatment of relapsing patients because of the significantly-higher response rates to Raptiva versus placebo: 31 percent versus 0 for PASI 75 and 67 versus 19 for PASI 50.

So this is the retreatment efficacy of Raptiva in relapsing patients. To complete the picture, we evaluated the efficacy, the retreatment efficacy of Raptiva in stable patients and found higher response rates. I can present the details of those results to the committee in the question and answer period, if you'd like.

I'll now finish with our final conclusion. The efficacy of Raptiva improves with continuous treatment past 12 weeks. The evaluation of efficacy past 12 weeks relies on study 2390 and its extension study 2391. Patients who completed study 2390 were eligible to enroll in study 2391 and received Raptiva 1 milligram per kilogram per week for 12 weeks. The evaluation of the efficacy past 12 weeks focuses on these 369 patients and follows them through study 2391.

Now, recall that in the assessment of the week

12 response rates, patients who discontinued were considered to be non-responders. So this same conservative intent-to-treat approach is taken in the assessment of the week 24 rates. So patients who dropped from 2390, failed to enroll in study 2391 or dropped from 2391 are considered to be non-responders in the week 24 analysis.

This chart shows the PASI response rates at week 12 and week 24 for these 369 Raptiva-treated patients. The results at week 12 you've seen before: 27 percent PASI 75 rate, and 59 percent PASI 50. At week 24, the PASI 75 rate increased dramatically to 44 percent, and the PASI 50 rate increased to 66 percent. Both of these increases, 27 to 44 percent and 59 to 66 percent, are highly statistically significant.

So this conservative intent-to-treat approach, the high statistical significance of the increases, and the large increase in the rate of PASI 75 response represent strong evidence that the efficacy of Raptiva improves with continuous treatment past 12 weeks.

Importantly, we have confirmation of this 44 percent PASI 75 rate in a separate study of 339 patients who are with this same conservative intent-to-treat approach. The PASI 75 rate at 48 weeks of treatment was 45 percent.

In summary, our clinical program allowed us to

thoroughly evaluate the efficacy of Raptiva. We learned that Raptiva at 1 milligram per kilogram per week for 12 weeks has significant and clinically-meaningful efficacy. At 12 weeks, the PASI 75 response rate was 27 percent and the PASI 50 rate was 59 percent. Patient quality of life and symptoms all improved. Raptiva has an early onset of efficacy with efficacy demonstrated 4 weeks after the start of treatment.

Regarding intermittent treatment, when Raptiva is stopped, psoriasis returns and the median time to relapse is about 2 months. Raptiva is effective on retreatment and patients who respond well to a first treatment with Raptiva are likely to respond well with retreatment.

Regarding continuous treatment, in contrast to the loss of efficacy when Raptiva is discontinued, the efficacy of Raptiva improves with continuous treatment past 12 weeks. We observed a PASI 75 response rate of 44 percent at 24 weeks and 45 percent at 48 weeks. Taking all the data together, we conclude that Raptiva is most effective when used as continuous treatment.

This completes my presentation. Thank you for your attention. I would now like to introduce Dr. Richard Chin who will summarize the safety of Raptiva.

DR. CHIN: Good morning. It's a pleasure to be

here. My name is Richard Chin, and I'm the Director of Clinical Research for the Specialty Biotherapeutics Unit at Genentech.

What I'd like to do today is to review the Raptiva safety data and demonstrate that Raptiva is a very safe and well-tolerated drug, supported by a large and robust database.

This is the outline of my presentation. I'll begin with an overview, then I'll discuss the clinical adverse events during treatment and after treatment. I'll then discuss the laboratory findings, followed by the extended treatment data. Then I'll conclude with a summary.

The key points from my presentation are summarized on this slide. First, Raptiva has been extensively studied in a large number of patients. Second, Raptiva has a low overall rate of serious adverse events. 2 percent in the 1 milligram per kilogram group which is our recommended dose. Third, Raptiva was well tolerated. The dropout rates were low and the most common adverse events were mild and self-limited. Fourth, Raptiva's safety profile over the extended treatment period appears as favorable as its safety profile over the short term.

As was previously mentioned, the Raptiva clinical program was large. There were 2,762 patients in

the psoriasis clinical program and out of these, over 900 patients were treated for 6 months or longer. Over 200 patients were treated for 1 year or longer. There were a total of 1,790 patient-years of Raptiva experience in the clinical program, and the significance of these large numbers is that this gives us high power to detect even rare events.

I should note that most of the data that I'll be presenting today is based on the BLA that was submitted to the FDA. Since the submission of the BLA, we have accumulated significant additional patient-years of experience and the safety profile has not changed with the additional data.

As Dr. Rohrer has mentioned, there were 13 clinical trials in the Raptiva program and out of these, 4 were randomized double-blind placebo-controlled phase III studies. These studies are highlighted on this slide and wherever possible, I'll be using the data from the placebo-controlled studies.

For rare events, I'll be using the entire database in order to increase our power to detect rare adverse events. When I do so, I'll be expressing the rates in terms of patient-years, and this is because although we have nearly 200 patient-years of placebo experience, we have nearly 1,800 patient-years of Raptiva experience. So

in order to draw meaningful comparisons, I'll be using patient-years where appropriate.

Also, for very rare events, I'll sometimes be referring to external epidemiological cohorts to provide an estimate of the expected background rate.

I'd now like to discuss the clinical adverse events beginning with adverse events during treatment.

This table summarizes the common adverse events seen in the placebo-controlled period which is the initial 12-week period. The first row represents the overall adverse event rates. These include all events, mild, moderate, severe, drug-related and non-drug-related. As you can see, the rate in the placebo group was 73.6 percent, the rate in the 1 milligram per kilogram group, which once again is our recommended dose, was 82.4 percent, and the rate in the 2 milligram per kilogram group was 87 percent. So slightly higher in the Raptiva group.

The other rows in this table represent all adverse events that were seen in at least 5 percent or greater number of patients in any dose group and occurred at at least 2 percent higher frequency in the 1 milligram group compared to the placebo group. As you can see, it's not a long list and most of these events are components of what we have called acute adverse reactions.

Acute adverse reactions are mild flu-like

reactions that are not uncommonly seen with biologics, particularly with antibodies. They tend to be self-limited and they tend to occur with the first dose or doses. For Raptiva, these reactions were prospectively defined as headache, fever, chills, nausea/vomiting, or myalgia that occurred within 48 hours of a Raptiva injection, and as you can see, with the first and second doses, the rates are different between the Raptiva and the placebo groups. However, with the third and subsequent injections, the rates are essentially identical. In general, most of these events are mild and self-resolved or at most resolved with Tylenol or nonsteroidals. They also tended to be short-lived with a median duration of 1 to 2 days.

With regard to serious adverse events, the rates were low and similar across the dose groups. The first row on this table is the overall serious adverse event rate during the placebo-controlled period. As you can see, the rate was 1.7 percent in the placebo group, 2 percent and 2.9 percent in the Raptiva groups. The other rows in this table represent all serious adverse events that were seen in at least 2 patients during the placebo-controlled period.

The key take-aways from the table are: one, there's no consistent pattern with respect to the types of adverse events; two, there's no clear dose response; and

three and most importantly, the rates of these events in general were low.

Next, I'd like to discuss some specific topics. As you know, many immunosuppressive drugs have the potential to cause increased risk of malignancies and infections. Raptiva is an immunosuppressive agent and therefore these were the two types of events that we paid particular attention to in our clinical program. Thrombocytopenia was observed in a few patients in our clinical program. These events may or may not have a causal relationship to Raptiva and I'd like to discuss that. Psoriasis and arthritis adverse events were also seen in a few patients in our program and I'd like to discuss that as well.

With respect to malignancies, the rates were low and similar across the dose groups. The rates expressed here are in terms of rate incidence per 100 patient-years. The rate in the placebo group was 1.62, in the Raptiva group 1.68, so very similar. With respect to the individual types of malignancies which are broken out in this table, the rates in general were similar between the placebo and the Raptiva groups.

Now, given the long latency period for malignancies, we should be cautious in interpreting this data. However, the key take-away is that the rates are low

and similar between the placebo and the Raptiva groups.

With respect to infections, the infection rates were balanced across the placebo and the Raptiva groups as well. 26.3 percent in the placebo group and 28.9 and 28 percent in the Raptiva groups. This is shown in the top row of this table. The rest of the table lists the most common types of infections. The most common type of infections were nonspecific infections or miscellaneous infections. Most of these were colds and upper respiratory infections. As this table shows, the other rates in general were low.

With respect to serious infections requiring hospitalizations, there was a slight trend towards a higher rate in the Raptiva group: 1.18 versus 1.61 per 100 patient-years. It's important to note that the placebo rate is based on just 2 patients, so the confidence interval is large. Because of this, we compared the rates to an external epidemiological cohort of psoriasis patients, and from this, we found that the Raptiva rate did not appear to be elevated compared to the expected background rate.

Importantly, there were no deaths between infection, less than 1 percent of the patients discontinued Raptiva due to an infection, and most patients, even patients who were hospitalized for infections, continued

Raptiva or at most had one or two doses held.

With respect to unusual or serious infections, there was one case of Legionella in a patient taking the 2 milligrams per kilogram dose. This patient recovered fully without sequelae and the case occurred in a community where there was a small outbreak. Obviously the other patients were not receiving Raptiva. It's very important to note that even given our high power to detect rare events, we did not see other opportunistic infections, such as tuberculosis, PCP, or other infections listed here.

We did see a few cases of somewhat atypical or severe infections, such as vertebral osteomyelitis and severe sinusitis. We should note that these cases were very rare and occurred in a large database of nearly 3,000 patients, so it's not clear that this represents a true signal, but even if it did, the rates would be very low.

Now, in our program, we did see some rare reversible thrombocytopenia. There were 8 patients who developed either a serious adverse event of thrombocytopenia or had a platelet count below 50,000. Out of these 8 patients, 6 patients had a course that was consistent with a drug-induced effect. The two additional cases had clear other causes. One patient had prior documented history of ITP, the other patient had prostate cancer.

Out of these 6 patients, all had rapid recovery of their platelet count when Raptiva was discontinued. Most of the patients had corticosteroids initiated. The lowest platelet count ranged between 3 and 52,000 and 3 of the patients had clinical manifestations. One patient had hypermenorrhagia, another patient had intermittent rectal bleeding, and a third patient had bleeding with scratching. All recovered clinically.

Now, causality has not been established. They certainly be causally related to Raptiva. However, in 4 of the patients, there were potential other causes, such as viral syndromes, Grave's disease, other medications. However, we feel that it's prudent to err on the side of caution and we feel that physicians and patients should be warned or advised to watch for signs of bleeding, such as gum bleeding, petechiae or easy bruising. Genentech is also committed to further studying thrombocytopenia in the post-marketing setting to further understand this issue, if Raptiva is approved.

As I previously mentioned, we saw some patients with psoriasis adverse events in our program. Psoriasis adverse events were defined during our studies as a psoriasis event that was unusual or not typical for that patient's disease. Most of these events were seen after discontinuation and I'll be discussing that later in my

presentation, but a few did occur during treatment. The rate of these events during the placebo-controlled period was 1.4 percent in the placebo group and 3.2 percent in the Raptiva group.

It's important to note that the rates declined with extended treatment, and also the most frequent type of events were mild to moderate guttate psoriasis. Wery few patients discontinued Raptiva due to these events. However, there were 5 patients out of the 2,762 treated patients who did develop a serious adverse event of psoriasis. 4 of these patients had erythrodermic psoriasis. All the patients did recover without sequelae.

In addition, there were a few patients during treatment who experienced an arthritis adverse event. The rate in the placebo group was 2.2 percent and in the 1 milligram group was 2.4 percent. The rate in the 2 milligram group 3.9 percent. Most of the events were mild to moderate in severity and the vast majority of these patients had prior history of arthritis. Also, the rate did not increase with extended treatment. So during treatment with Raptiva, the incidence of arthritis was low and comparable between the placebo and the Raptiva groups, particularly with respect to the 1 milligram group which is our recommended dose.

Next, I'd like to discuss clinical adverse

events after treatment. As was previously mentioned, Raptiva is a reversible drug which, in many respects, is a positive attribute, but because of this, when it's discontinued, psoriasis returns. In a minority of patients, it does return to a state worse than baseline and I'll be discussing that shortly. However, it's important to note that for the vast majority of patients, the return of psoriasis is gradual and they do not get worse than baseline. This is illustrated on this plot of mean PASI improvement over time.

It's also important to keep in mind that the Raptiva studies were designed in a very rigorous fashion and imposed strict restrictions on concomitant medications during the withdrawal period. For example, immediate transition to other therapies were not allowed and taper of Raptiva was not allowed. Initially in the program, even when patients started losing some of their benefit, systemic therapies were not permitted. This was changed later in the program as we learned more about Raptiva and patients in the later portion of our program were permitted to start systemic therapies if they lost 50 percent of their PASI improvement.

With this in mind, 13 percent of the patients did experience a psoriasis adverse event during the 12-week follow-up period after discontinuation of Raptiva. Most of

the events were mild to moderate in severity and approximately half were recurrence of plaque psoriasis. However, 14 patients, or less than 1 percent of the patients, did experience a serious adverse event of psoriasis. Most of these patients were non-responders. Most had received more than 1 milligram per kilogram dose and approximately half of the patients had erythrodermic psoriasis and approximately half had pustular psoriasis. All the patients recovered without sequelae.

I should mention that Dr. Lebwohl and Dr. Menter who have each treated a large number of patients with Raptiva and each of whom have had a patient with an erythrodermic event are available to answer any questions you might have.

Our conclusion from our experience with Raptiva is that it's not advisable to discontinue Raptiva without observing patients carefully or transitioning them to other therapies.

Now, we have a formal transition study that's currently ongoing and the data is not available yet. What we do have is an analysis from the subgroup of patients who did start other medications during the withdrawal period.

Now, I need to be clear. These are not patients who were transitioned immediately to other therapies which is what we would recommend. These are

patients who happened to start other therapies some time during the withdrawal period.

So this is a table of psoriasis adverse events, excluding mild events, and as you can see, patients who received other medications had rates that were lower, as low as 0 percent, with some of these medications. We need to be cautious in interpreting this data because this is non-randomized data and it's observational data. However, the data is suggestive that indeed transitioning patients to other therapies may lower the likelihood of having these events.

So, in summary, there were psoriasis adverse events after completion of Raptiva therapy, a small number of which were serious. Our clinical trials were conducted in a very rigorous manner which may have increased the rates of these events, and in clinical practice, the rates may be substantially lower. Regardless, we think that it's important to advise patients and physicians to observe for signs of flare after discontinuation of Raptiva, and ideally patients should be transitioned to other therapies.

With regard to arthritis adverse events, 4.9 percent of the patients experienced an arthritis adverse event after Raptiva therapy. The rate was 3.7 percent in the 1 milligram group. I should remind you that the placebo rate during the placebo-controlled period was 2.2

percent. 7 patients, once again less than 1 percent of the patients, did develop a serious adverse event of arthritis. As I mentioned, most of these patients were discontinued from Raptiva without transition to another therapy. And the data suggests, but is not conclusive, that arthritis may return, similar to psoriasis skin disease, in a very small number of patients if Raptiva is discontinued without transition.

Next, I'd like to discuss the laboratory data. The most common laboratory finding was mild leukocytosis. This is consistent with the mechanism of action of Raptiva. The leukocytosis was readily reversible upon cessation of therapy.

A few patients had mild elevation of alkaline phosphatase which was never more than 2.5 times upper limit of normal and in general, these were not associated with concomitant increases in SGOT or SGPT. Also, these were not associated with clinically-relevant findings.

Also, a few other patients had elevations in C-reactive protein and these were not associated with clinical findings either.

Importantly, there were no signs of organ toxicity.

Next, I'd like to discuss the extended treatment data. As was previously mentioned, the current

treatment paradigm for psoriasis is rotational therapy because of the concern for cumulative toxicity. Therefore, long-term safety data in a drug such as Raptiva is important.

These are the rates of overall adverse events, infections, and serious adverse events expressed as rate per 12-week period. As you can see, the rate of overall adverse event rates, which is the top line, appears to decrease or at most not increase over time. The rates of infections and serious adverse events appear to remain constant over time. So based on this data, Raptiva's safety profile is maintained with extended treatment

Also, there were no new safety signals that emerged with the extended treatment, and with regard to specific types of adverse events, there was no increase in any particular type of adverse event over time.

Now, we recognize that although Raptiva has been extensively studied, there are remaining questions that are best answered in a post-marketing setting. Genentech is committed to conducting the necessary studies post-approval to further characterize the long-term safety profile of this drug if Raptiva is approved.

So, in summary, Raptiva was well tolerated. The most common adverse events were mild and self-limited. The rate of serious adverse events and malignancies were

low and comparable to placebo. The rate of serious infections was low and similar to the expected background rate. There were a few patients who developed reversible thrombocytopenia and a few patients developed psoriasis adverse events which on occasion were serious. There was no evidence of hepatic or renal toxicity, and the extended treatment safety profile appeared as favorable as the short-term safety profile.

Thank you very much, and I'd like to turn the podium back over to Dr. Johnson who will discuss the benefit-risk assessment.

DR. JOHNSON: Thank you.

Mr. Chairman, members of the committee. Psoriasis is a chronic lifelong disease which has been well described by Dr. Lebwohl and you know well as members of the committee. It has significant impacts on quality of life and functioning in these patients which has been equated to that impact had by other chronic diseases, such as diabetes and cancer and cardiovascular disease. The common symptoms of itching, pain, and bleeding impair the quality of life.

Topical medications are insufficient to treat the moderate to severe form of this disease, and although there are currently approved therapies, these have limitations in terms of cumulative toxicity and convenience

for the patient.

The drug that we have discussed today is a human monoclonal antibody which is dosed once weekly as a subcutaneous injection. It has a relatively early onset of action and it's effective at 12 weeks with PASI 75's of 27 percent and PASI 50's of 59 percent, as Dr. Kaiser has described, and with extended treatment over 24 weeks, we see the impression of improved efficacy as evidenced by the 44 percent PASI 75 result. We know that with long-term exposure up to 48 weeks, we can maintain that response at 45 percent in patients. We believe it is best used as continuous therapy.

This shows a patient with a dramatic response to the therapy, but the more important outcome is this impact that it has on the patient's quality of life. As Dr. Kaiser told you, almost 70 percent of that benefit is observable within the first 4 weeks, and there is continued improvement out to 12 weeks.

We have an extensive safety database with more than 2,700 patients treated. As Dr. Chin showed you, most of the common adverse events which are associated with this drug are typical of the types of events that we commonly see with biologics. They are onset, shortly after therapy, of mild flu-like symptoms following those first two Raptiva injections. We believe that these are eminently manageable

with the use of such medications as Tylenol and nonsteroidal anti-inflammatories.

Overall, there is a favorable adverse event profile, particularly with respect to infection and malignancy.

We believe that the psoriasis adverse events which Dr. Chin discussed in some detail are manageable and relatively infrequent. We have an understanding of when they occur and are able to change the management profiles such that we can prevent many of those.

There were some infrequent cases of reversible thrombocytopenia, and there was no evidence specifically of renal or hepatic dysfunction in these patients.

So we've shown meaningful clinical benefit demonstrated in patients with moderate to severe plaque psoriasis. Ongoing therapy with Raptiva provides extension of that benefit with no apparent increase in adverse events as the exposure is prolonged, but clearly the sample size that we are looking at in those long-term studies and those extended studies is relatively small.

We believe that the frequency of psoriasis adverse events on withdrawal can be mitigated by not continuing therapy in non-responders, by limiting that dose to 1 milligram per kilogram during the first 12 weeks of exposure, and in those patients who have not responded by

12 weeks, to transition to alternative therapies.

Based on the robust efficacy and the reasonable safety, we believe firmly that Raptiva should be made available as an alternative therapeutic option for patients with moderate to severe plaque psoriasis. We have committed to post-approval surveillance studies. I would just like to say that we at Genentech are very proud of our record with post-marketing registries, exemplified, I think, by the National Registry of Myocardial Infarction which is considered sufficiently objective by both the American Heart Association and the Joint Committee on Hospital Accreditation to be used for their guidelines.

That concludes our presentation, and I would leave you with the indication that we're requesting today that this drug should be available for the treatment of patients with moderate to severe plaque psoriasis, and at this stage, we'd be happy to take any questions or clarifications that you may require.

Thank you very much.

DR. STERN: Thank you very much. The meeting is open to questions from the panel.

DR. PLOTT: Could you explain why you did four phase III clinical trials? Normally two is what's requested in the regs. Could you explain why that was done?

DR. JOHNSON: Surely. I think that was explained in fact by Dr. Kozlowski in the opening remarks. It had to do with the fact that we transitioned from the Xoma-manufactured material to the Genentech-manufactured material during the phase III process, and because of the differences in pharmacokinetics, we made absolutely sure that the clinical effect of the drug was similar with the Genentech to-be-marketed material.

DR. STERN: Dr. Morison?

DR. MORISON: I just wonder whether you could comment on the surprisingly low secondary response. You took the patients who achieved PASI 75 and then followed them until they started to flare or relapse and then only 30 percent were able to get back to another PASI 75. That I find rather astonishing when you think about the other agents that we use. Why does this agent lose its effects so dramatically?

DR. JOHNSON: We were also puzzled by that. I think one of the things that we believe here is that when those patients are actively relapsing, when we reinstitute the therapy, what we saw if we looked at the mean PASI change over time, instead of when you treat a stable patient, you see a rapid drop in that PASI score.

In these particular patients, we saw a period of stabilization of that PASI score. In other words, we

were trying to stabilize them for their first few weeks of therapy, and then we saw the drop in PASI score.

So I think partly it's an artifact of the fact that these patients were actively relapsing and they took slightly longer to stabilize on therapy, and therefore if we had followed them out further, beyond the 12-week time point that we looked at, I think we would have seen better results.

DR. MORISON: So what you're saying but the word has not been used so far that I've noticed this morning is that this drug is prone to rebounds of psoriasis, just as we see with, say, methotrexate and other agents.

DR. JOHNSON: Yes.

DR. MORISON: In other words, once you come off the agent, people are going to be aware that a rebound of more aggressive psoriasis is very likely to happen.

DR. JOHNSON: Yes.

DR. STERN: But one difference, as I read these data, compared to at least historical experience with methotrexate is it would appear that when we reinstitute methotrexate when people are flaring, they respond again, almost all of them, because after all, you have selection. You're only talking about retreating responders, the 24 percent who reached PASI 75 in the first place; whereas

with this drug, as opposed to my expectation with psoriasis, that if you're flaring with psoriasis because you've had methotrexate withdrawn and it can be used again, the chances are very, very high you'll respond again; whereas here, the chances are about 1 in 3 a prior responder will respond to the reinstitution of therapy, which is different than clinical experience.

I'd just like to address one other methotrexate data. I think it was Dr. Lebwohl presented some unpublished data. In fact, in the New England Journal recently, there was a randomized controlled trial of methotrexate versus cyclosporine where I believe they showed that methotrexate and cyclosporine both had PASI 75's in the 60 to 70 percent range.

DR. JOHNSON: Perhaps I could get Dr. Lebwohl to respond.

DR. LEBWOHL: No. I think that you read that incorrectly. In fact, the median response to methotrexate, the average patient did not achieve a PASI 75. The mean reduction in PASI score was 63 percent in that article. It was a few weeks ago in the New England Journal of Medicine.

DR. KATZ: In that article, 60 percent of methotrexate patients received a PASI of 75. 60 percent.

DR. STERN: 60 percent.

DR. LEBWOHL: The mean reduction was 63

percent.

DR. KATZ: No. We're not talking about mean reduction.

DR. STERN: I believe it was 71 for cyclosporine. Is that your recollection? It was 60 for methotrexate and a little bit higher for cyclosporine.

DR. KATZ: I'm not talking about the mean reduction.

DR. STERN: Right. PASI 75.

DR. KATZ: The percentage of patients getting a PASI 75 was 60 percent. Now to be fair in that article, though, there was no placebo control. Methotrexate and Neoral were studied and compared and found to be equal, but 60 percent of methotrexate received PASI 75 which is consistent with clinical findings, at least consistent with clinical findings. Patients on methotrexate have, as we who have experience know, a very high percentage. There are other data in the literature. I can't quote articles. 85 percent get very satisfactorily improved.

As was emphasized by the chairman, the treatment effect by the FDA is PASI 75, and we keep bringing up PASI 50 where people are satisfied, but to put it in context in practice, a PASI of 50, I mean, you get that with very commonly noninvasive/nonsystemic treatment in many patients. So PASI 75 is really more vigorous.

The other thing, I think it's not fair when it summarized that 27 percent received a PASI 75 and then it recurs with other drugs. They forget about the placebo effect, not that it's very great in this instance, but the 27 percent really is not. People are interested in treatment effect, treatment effect defined as the drug effect minus placebo. So I think that percentage should be used to be fair in conclusions.

The other counterintuitive comment -- and I know it's used in the literature but we have to keep it in perspective -- is patient-years. One can accumulate a lot of patient-years with 6-month follow-up, 3-month follow-up. In the historical perspective, the drugs that have caused problems, many of them wouldn't be detected in patient-years with a 1-year study. Carcinogenesis or x-ray therapy, arsenic, PUVA. 6-month, emphasizing that.

The other thing is we do have only 200 patients that have been followed -- am I correct -- for 1 year.

DR. JOHNSON: 228, yes.

DR. KATZ: Yes. So we have to keep that in mind as well.

DR. JOHNSON: No, no. I absolutely agree with your comment. I think the use of the patient-years was an attempt to do the comparison. We're not claiming that we have 1,700 patient continual years of exposure. What we're

trying to say is that in order to do the appropriate comparison between the relatively short 12-week placebo period that we have and the slightly longer exposure which is an average of about 6 months on the active patients, we did the calculation that way, which I think is appropriate.

DR. STERN: I'd like to actually ask a question to clarify the data. I believe you have about 318 patients with more than 24 weeks of exposure. I'd like to ask a quantification question and then a follow-up question. What proportion of those were on continuous therapy for more than 6 months? Because as I understand it, you're asking for an indication for continuous therapy and with immunosuppressive therapy, having 24 weeks and two 12-week periods separated by a period of time from a safety standpoint is certainly different than having 24 or 36 continuous weeks.

So within our safety database, not how many were treated for 24 weeks, but how many were treated continuously for 48 weeks for each of these continuously as opposed to --

DR. JOHNSON: Right. So this data would show you the patients who are treated continuously and it suggests that we have 219 for at least 48 weeks, 500 for 36 weeks, and we have one study which we're planning to take out to 3 years, which is obviously ongoing and we continue

to collect data. But of the data that we have submitted to the FDA, we have a 153 patients who have been treated for at least 84 weeks.

DR. STERN: And this gets to the issue of real selection bias. It would appear that only responders, people without toxicity, continued to be treated and followed, and we heard, before which I found very interesting, that these were well-powered studies.

If we're looking for, as was mentioned, lymphoma and non-melanoma skin cancer and we're looking for -- do you have any idea about what the power calculations would be, in fact, to detect a relative risk of 2 or 3 compared to expecteds?

DR. JOHNSON: I would absolutely agree with you, sir. Clearly, we have insufficient power to detect events with a longer-term latency. So what I would say is that as we do the comparisons right now with the control period, which is common at this stage of development, we do not see a signal. I think also importantly, we've looked very carefully at our preclinical data in terms of the ability of this molecule to stimulate lymphoma to change in known models, and contrary to drugs such as cyclosporine, we see no effect in our preclinical models of that drug, which is reassuring but not definitive.

DR. STERN: Andy.

DR. BLAUVELT: In the greater than 200 patients that were treated for more than a year, I would have liked an analysis of just those patients and the rare events, infections and cancers, that developed in that group, and I didn't see that in the presentations. We just heard that no additional signals were identified, but I would have liked to have seen a discussion of the rare events in the greater-than-1-year treated group.

DR. JOHNSON: Could I see the adverse events by time to treatment? So let me see the serious adverse events by time to treatment.

So if we show this next slide, this is serious adverse events over time. I can show you other data of specific questions, if you would like, but what we see in terms of skin cancer is that there's no apparent increase with extended treatment. Obviously these numbers, as you've pointed out, are relatively small, but the rates do not appear to change significantly over time.

I will say that we looked very carefully at the skin cancers during the study and we are looking at their baseline associated factors. We saw that they tended to be clustered in those patients who had previously received methoxycillin and ultraviolet light, and certainly there was a preponderance of people who had previous skin cancers in that group. So those are both known predictors of skin

cancers.

DR. STERN: Could we perhaps see your data separating out basal cell and squamous call carcinoma of the skin? Lumping all skin cancers or all non-melanoma skin cancers is really not very much to the point for what we know about the concerns of immunosuppression and carcinogenesis in the skin. So do you have those data separately?

DR. JOHNSON: I don't have them separately. I can tell you that the ratio of squamous cell cancer to basal cell cancer was 1 to 1, I think a relationship that other people have described in these types of patients.

DR. STERN: I think the other people who have described those have noted that as in fact evidence of a carcinogenic treatment effect, and I think those same individuals might well suggest that not much happens or nothing happens within a year, unless you have a population that is prime to go, the classic example being pretreatment with high doses of PUVA and then exposure to an immunosuppressive agent. As I recall, in terms of the distribution of prior exposures in your population, you did not have a large number of previously-treated PUVA patients. You had some. And I don't recall any quantification of their level of exposure because less than 200 PUVA treatments, at least as I recall, was not

associated with an immediate effect of immunosuppression, not that it wouldn't be in the longer term.

DR. JOHNSON: Let me just show you then the data that we have. We did not actually specifically collect a great deal of information on the amount of previous therapies that people had had, but we were able to see that if you look at the prior exposure to PUVA, 50 percent of the skin cancer cases, compared with only 34 percent of all patients, had had previous exposure to that therapy. As I said, the previous history of non-melanoma skin cancer was significantly higher in this subpopulation than in the overall population.

So I think you're absolutely correct to point out that we don't know the answer to this yet and it will take some prolonged follow-up, but I think that these data are relatively reassuring.

DR. STERN: Andy?

DR. BLAUVELT: I'll switch off to safety, I guess, for a second. Like most drugs, we don't know why certain patients respond and others don't. Have there been any attempts -- I haven't heard anything yet -- to try to discern, for example, why certain patients would respond or not?

I could think of several things. Have there been any ex vivo analysis of T cells from treated patients

to see if there's less ability to activate them? Do they adhere less well to endothelial cells? You could also think possibly of polymorphisms and CD11a that may affect binding of the antibodies. So have those things been done?

DR. JOHNSON: Perhaps the best thing for me to do here would be to ask Dr. Krueger to come and comment on that since this is particularly his area of expertise, if that's okay with the committee.

DR. KRUEGER: What you identify is actually somewhat of a vexing problem to me across all of the biologics, and that is, we have groups of patients that respond really well and other groups of patients that don't.

I spent a number of years trying to study this problem and have gotten to the following level. It's not a simple issue of polymorphism and CD11a or differential binding of the antibody. Everybody has saturation. Many of the effects on cell adhesion are very similar in peripheral blood.

I think where the differences lie are with the effects of the antibody on cells that have migrated into tissue, and what we see is the people who respond really well are people that both have a higher magnitude of T cell reductions in tissue and also suppression of inflammatory cytokine production from the cells that are there.

So there is this dichotomy and I think it goes to the nature of trying to be very selective in immune suppression as opposed to rather broad with something like cyclosporine where you hit multiple pathways very solidly, and here you're hitting only one of several inductive pathways for T cell activation. I think polymorphism genetics across people may determine whether blockade of this in one person versus another turns off a T cell to a certain degree.

DR. BLAUVELT: Just to follow up. So have there been ex vivo analysis of the T cells of these treated patients to show that T cells from responders are activated less well compared to T cells of non-responders?

DR. KRUEGER: Well, I've done the in vivo analysis of T cells in tissue by RT-PCR and cytokine production and histology. I've done a little bit of ex vivo analysis of peripheral blood cells and there's not much differential signal with any of the peripheral blood test. There is a big difference in tissue.

DR. STERN: Dr. Morison?

DR. MORISON: While you're there, I have a question for you. We've shown the histo slides through 12 weeks, I think it was.

DR. KRUEGER: Yes.

DR. MORISON: 8 weeks. The thing that strikes

me is that when you look at the slide for 8 weeks, it wasn't really normal skin. It was still psoriasis in terms of the number of lymphocytes and in terms of the acanthosis. I'm just talking about general terms. It wasn't back to normal skin. If you look further out than 8 weeks, does the skin just simply histologically get back to normal?

DR. KRUEGER: Let me say, though, that the change that we've seen which is thinning of the epidermis, reversal of keratin 16, probably does improve a bit more with treatment, but frankly, if you look at all of the therapies that we throw at psoriasis, except for something like PUVA that is totally depleting for lymphocytes in tissue, almost all of the resolution of psoriasis is with some increased acanthosis over what you would see in totally normal skin.

So we've turned off the inflammatory pathway. We've turned off hyperplasia. We haven't absolutely restored the tissue back to what normal skin looks like, but I don't think there is any therapy that does that.

DR. MORISON: So that's why probably you're getting rebounds in these patients?

DR. KRUEGER: Not all the lymphocytes are gone. Certainly this is not a lymphocyte-depleting therapy, unlike some others, and I think you have to think of it

sort of like cyclosporine and that is, you take it away and the lymphocytes reactivate.

DR. EPPS: I just have a question about the people who dropped out. I know they were categorized as non-responders, but what happened to those people? Why did they drop out? What happened? Was there a follow-up of those people?

DR. JOHNSON: Well, I think the most important thing when you do these studies is to, A, look at the proportion of patients who drop out of the studies to be sure that the studies are relevant and you're not missing too many patients, and then you look specifically at the number of patients who dropped out because of adverse events.

The dropout rates overall -- I can show you for the various studies -- ranged between 6.5 and 9 percent which over a period of -- well, the 2058 studies and the 2059 studies were very complex studies. It's not unreasonable. If you look at the adverse events which related to dropout, they were slightly higher in the active treatment group than in the control group, the control group being approximately 1.5 to 2 percent and the active group being 2 to 2.5 percent.

DR. EPPS: But do you have any reason why they dropped out?

DR. JOHNSON: Yes.

DR. EPPS: That's my question.

DR. JOHNSON: So 2 to 2.5 percent of them dropped out because of adverse events, such as headache or failure to respond to the therapy and things like that, but these are the sort of rates that you would expect to see in most clinical programs.

DR. STERN: Dr. Drake, then Dr. Plott.

DR. DRAKE: I'd like to refer this question I guess probably to your dermatologic experts. I've been on this committee for a long time in different capacities and I'm not certain that I agree with Dr. Stern's opening comments, that unless it's a PASI 75 percent, it doesn't count. There have been meetings of this committee without any drugs being considered at all to just determine how we evaluate psoriasis and what the PASI scores need to be and how reliable is the PASI as a measurement. I'm not getting into that debate, Rob. I understand you asked us not to.

On the other hand, I don't think we can rule out 50 percent improvement in the PASI score because the PASI is not that exact, and I think we should consider it, but that's my personal sense of the moment right now.

So I would like to refer to people who are legitimately experts in psoriasis, such as Dr. Lebwohl and Dr. Menter, and ask them their opinion on the state of the

art because they, too, have followed this notion over the years of how we evaluate and I would like them to comment on that, please.

DR. LEBWOHL: Certainly when quality of life surveys are done, the additive benefit from going from a PASI 50 to a PASI 75 is small. Most of the benefit comes with the PASI 50. So in terms of the patient's point of view on questions that are asked, a large proportion of the benefit comes from achieving a PASI 50.

I will say, also, there's no question methotrexate is a dramatic, effective drug. And I did look. The mean response of that was 63 percent. I didn't realize that the PASI 75 was 60 percent. It's very difficult to compare one study to another and certainly difficult to compare someone performing a PASI score when no one is looking over their shoulder versus a drug study monitor looking over their shoulder, but methotrexate is a dramatically effective drug and if we could have the kind of effect that we get with methotrexate without some of the side effects, I think that that would be a desirable outcome.

But certainly the PASI score -- I think Dr. Stern I can quote as saying PASI is passe or something like that -- is a difficult tool. If somebody is severe and you grade that as a 3 and they're severe all over and then they

go to a 1, to mild, all over, the patient may be thrilled, and in fact the perfect example is you'd look at that and say, well, this patient's cleared, and if no one was looking over your shoulder, you might rate that in a trial as 0. Well, if you know that somebody is going to be looking at photographs and there's any psoriasis left, you have to rate it a 1. Well, then you've gone from a 3 to 1. That's only 67 percent improvement in PASI score. You don't get a PASI 75 then.

So the PASI is a difficult tool and it is a good tool if it's understood correctly, but a PASI 75 is a very high bar. A PASI 50 is very good response.

DR. STERN: Dr. Menter?

DR. MENTER: Mr. Chairman, members of the committee, ladies and gentlemen, and I think some patients who are here as well, I think Dr. Stern really said it right and I'm quoting him in his introductory remarks when he said, "The aim of psoriasis therapy obviously is clear or almost clear," and I think all of us would love to get to that stage with the majority of our patients. The second point that he made was "keeps on working."

Having been around in the trenches, as Dr. Stern and many of us have been, for the last 30 years dealing with the question of PASI 75 versus PASI 50, I think the gold standard still has to remain PASI 75 because

this is where every study has gone. Do we as clinicians and investigators like it? The answer is probably no. Do we do it? Yes, we do. Do we do it in clinical practice outside of studies? Probably most of us don't do it.

On the other hand, bearing in mind the New England Journal of Medicine article that Dr. Katz and Dr. Stern alluded to, having a PASI 75 of 60, which we all I think recognize we get with methotrexate and cyclosporine, the big question is, is this achievable with this drug or the other drugs outside of methotrexate or cyclosporine?

I think I'm a little more reassured with the PASI 75 data, specifically answering Dr. Drake's question, by the fact that with continued treatment and not abruptly discontinuing this drug and possibly destabilizing a small percentage of patients, that we do get up in 24 weeks in a significant number of patients to a 44 percent PASI 75 with maintenance continuous treatment.

The big concern that Dr. Morison mentioned relating to the fact that this drug does cause a small proportion of rebound is, I think, very significant and important. Having had patients as Dr. Lebwohl has had, we notified the company very early on in the clinical studies that this was an issue and hence the transition study was started. It's my firm belief that since that has been done, our ability to ensure, as with methotrexate, that

patients do not rebound either by transitioning them to another treatment immediately or even overlapping for a couple of weeks, like we do in clinical practice, has prevented, in my hands and I know in a lot of the other clinical researchers' hands, this potential risk of rebound.

Thank you.

DR. STERN: Dr. Plott?

DR. PLOTT: Well, you answered part of that question, but my question had to do with the risk and benefits of continuous therapy versus intermittent therapy, because your efficacy slide number 24 in comparing that to your efficacy slide number 27 kind of gives you an idea of what the intermittent therapy might be like versus the continuous therapy and the numbers maybe aren't so different. I wonder if you could speak to some of that.

DR. JOHNSON: I think as Dr. Kaiser showed you on the slide you referred to, when you treat these patients, our experience in this one particular trial is that when you treated patients who were in active relapse, clearly the response rates were not as impressive as the response rates you saw in the second 12 weeks of continuous therapy.

Dr. Kaiser referred to another study that we looked at where we, in fact, allowed patients who had been

on previous trials of Raptiva to enter into another study, and if I may show that data. We looked in that study at three groups of patients. So this is a study which was an extension study. It was an open-label study, but it was in patients who had previously received drug, and the sort of rollover period between the previous study and this particular study was anything from 37 days to a number of months.

What we saw here was actually not the same result as the study we saw in the actively relapsing patients. So these patients were clearly relatively more stable and the overall response rate that we got is 36 versus 69 which is consistent with the data we've shown for the controlled portions of the studies, but when you look at those patients who previously had a greater than 75 percent response, you see dramatically higher response rates in that subpopulation and clearly very low response rates in people who were less than 50 in the original study.

So this suggested to us that it is the clinical picture in which you reinstitute that retreatment which may affect the outcome.

DR. TAN: I have a question on the onset of efficacy. So do you have risk data presented in terms of PASI 50 or PASI 75 instead of the actual mean and the

standard deviation percent improvement? Because PASI 50 or PASI 75 is what we're talking about in terms of efficacy.

DR. JOHNSON: Perhaps I should refer to Dr. Kaiser who can talk about the statistics of how we analyzed the studies.

DR. KAISER: May I have my core slide of the PASI percent improvement over time, the mean percent improvement? It should be in the onset of efficacy portion, yes.

So I believe the question was what would be the results if we analyzed the mean percent improvement over time as opposed to dichotomizing the variable into a PASI 50 and PASI 75?

DR. TAN: No. For example, at week 4, what is the proportion of patients who have achieved PASI 75?

DR. KAISER: We do have the PASI response rates broken out over time.

DR. BLAUVELT: He doesn't want to see the mean. He wants to see the percent, the absolute.

DR. KAISER: The PASI 75 by visit is shown here, and if we perform that same type of statistical analysis, we would see statistical significance at week 6. The same approach with the PASI 50 over time would show statistical significance at week 4.

DR. TAN: Do you know roughly what the p value

is at week 6?

DR. KAISER: At week 6, it's less than .05. I don't know the specific number.

DR. STERN: Dr. Ringel. I think we're already over time, so this will be the last question until our break.

DR. RINGEL: I'm interested, once again, in the issue of rebound, rebound being to my mind a PASI score that is over what their baseline was when they started the study. So my question is: what percentage of patients after the 12-week washout period have a PASI score that's greater than their baseline?

DR. JOHNSON: Yes, I can answer that question for you. So we obviously looked at the change from baseline in the PASI score, and this slide shows you over the 12-week washout period what proportion of patients who had the 25 percent over their original baseline. So it's 17.8 percent after 12 weeks of no therapies would have gone back over that PASI score. The placebo group does that during the first half of the trial. During the second half of the trial when we're washing out from Raptiva, the rates are similar in terms of the number of patients who go over 25 percent. Sorry. I should quickly rephrase that thing since I got it wrong the first time.

So during the washout period, the 143 patients

who went through to 12 weeks, 18 percent of them went over 25 percent of their original baseline. If you look at a comparable cohort -- so in other words, the people who are randomized to placebo in the first 12 weeks -- 17.8 percent of them go 25 percent over their baseline after a period of no treatment of 12 weeks.

Dr. Menter was actually a member of the National Psoriasis Foundation Rebound Committee. So I'd ask him to comment on these data.

DR. MENTER: I think your point is very well taken, that over 25 percent overshoot of baseline PASI would be certainly considered rebound by whatever definition you use.

I think the critical thing with this drug as with methotrexate and with cyclosporine is that abrupt discontinuation after 12 weeks, as we had to do in a clinical trial, is certainly not the way that we should be using this in clinical practice, and I would strongly urge that should this drug be approved, that we certainly educate our colleagues, as we have tried to do with methotrexate and cyclosporine, not to abruptly discontinue to allow rebound to happen.

In the transition phase studies, as I mentioned earlier, this issue of rebound appears to be completely a non-issue as it is with methotrexate and cyclosporine if

one tapers and transitions the drug.

DR. STERN: Thank you. We'll now take a 20-minute break and resume at 10:30.

Thank you.

(Recess.)

DR. STERN: We'll reopen the session with a presentation from the FDA by Dr. Papadopoulos on their review of efficacy and safety results of this product.

DR. PAPADOPOULOS: Mr. Chairman, ladies and gentlemen, members of the committee, good morning and welcome to Maryland.

On December 27th, 2002, Genentech submitted to the Food and Drug Administration their biologic license application for efalizumab. The proposed indication is for the treatment of adult patients with moderate to severe plaque psoriasis. The proposed dose is 1 milligram per kilogram per week administered subcutaneously and the proposed mode of use is as a long-term continuous treatment.

Before reviewing the safety and efficacy data, I would first like to take a moment to describe the demographics and characteristics of psoriasis. Psoriasis affects 1 to 3 percent of the U.S. population. The predisposition to psoriasis is polygenic inheritance with environmental triggers. It affects primarily caucasians

and is infrequent in Native Americans, African Americans, and Japanese. Psoriasis is thought to affect men and women equally. The onset is bimodal with one peak in individuals in their late teens and early adulthood and a second peak in individuals later in life.

As we have discussed, psoriasis has a bimodal peak. Early onset, before the age of 15, occurs in an estimated 27 percent of patients with psoriasis. When psoriasis occurs in childhood, it has an irregular course and is thought to have more severe disease expression. Early onset is closely linked to HLA-Cw6 positivity and 50 percent of patients have first-degree relatives with psoriasis. Therefore, there is a need for clinical trials in therapeutics of anti-psoriatic agents in children.

Although psoriasis is usually not life-threatening and the estimated 30 percent of patients with moderate-severe disease, it is associated with significant morbidity. It has also been reported that there is a decrease in quality of life and an increased risk of suicide.

Next, let us consider the clinical trials leading to this submission. Let us first begin with what we learned from the phase I and II studies in psoriasis with efalizumab.

This table summarizes the phase I and II

studies of efalizumab in moderate to severe psoriasis. These studies evaluated relatively short durations of treatment, most were less than 12 weeks, and limited numbers of patients were evaluated.

Earlier studies evaluated intravenous mode of administration before the change to the subcutaneous route that was used in the phase III studies. It was from these studies that we learned important safety information. It was determined from single-dose studies that dose-dependent adverse events, including meningismus, headache, nausea, vomiting, fever, chills, myalgia and arthralgia, occurred shortly after intravenous infusion with efalizumab. These adverse events were more common after the first dose and hence they were called the first dose effect. These dose-dependent adverse events led to the development of an initial low tolerization dose of .7 milligram per kilogram subcutaneously and this is followed by the 1 milligram per kilogram weekly subcutaneous dose.

Next, let us consider the phase III trials. There were four randomized placebo-controlled phase III trials. This table summarizes the phase III randomized, double-blind, placebo-controlled trials of efalizumab in moderate to severe psoriasis and serves as an overview of the trials that I will talk about. Two doses were compared in studies 2058 and 2059, the 1 milligram and the 2

milligram per kilogram dose. As we have heard, the 2 milligram per kilogram dose was not found to be superior to the 1 milligram per kilogram dose and was not further studied.

Two phase III studies shown here studied exclusively the Genentech-manufactured efalizumab. These were 2390 and 2600. Despite the differences in pharmacokinetics discussed earlier by Dr. Kozlowski, our analyses did not suggest any differences in the safety or efficacy between the Genentech- and the Xoma-manufactured efalizumab. So it is appropriate to consider the data as a whole.

We will start by describing the results from 2390, the pivotal study confirming the efficacy of the Genentech-manufactured efalizumab. Studies 2058 and 2059 had similar study designs and entry criteria and are supportive studies. In addition, we will further discuss retreatment using study 2058 and extended treatment using study 2059.

Study 2390 was the first phase III study evaluating exclusively the to-be-marketed efalizumab. It is a double-blind randomized parallel group multi-center trial. The dose evaluated was the 1 milligram per kilogram per week subcutaneous dose administered over 12 weeks. The duration of the trial was 12 weeks, and afterwards,

eligible patients could enroll into an open-label extension study 2391 without treatment interruption. Patients were randomized 2 to 1 to receive efalizumab or placebo. Randomization was stratified by baseline PASI and a history of systemic anti-psoriatic therapy.

The primary efficacy endpoint was the proportion of patients achieving a 75 percent improvement in PASI at day 84. The principal secondary endpoint was the proportion of patients achieving minimal or clear by the static physician's global assessment. Both the primary and the principal secondary endpoints were similar in the phase III efficacy trials.

Eligible patients were adult patients with plaque psoriasis involving at least 10 percent of the body surface area and having a minimum PASI score of 12. Patients with guttate, erythrodermic, and pustular psoriasis at baseline were excluded. Patients were to have chronic psoriasis diagnosed for at least 6 months. In addition, in this study, patients with a clinically significant psoriasis flare at screening were excluded. In the earlier studies 2058 and 2059, patients were, in addition, required to be clinically stable for 3 months prior to screening.

556 patients enrolled into this study. 187 were randomized to placebo and 369 to efalizumab. The mean

age was 45 years. Most of the patients were caucasian, 90 percent. The gender distribution included 69 percent men and 31 percent women. The two treatment groups were comparable with regard to baseline demographics.

Baseline disease characteristics are shown here. The mean duration of psoriasis was 19 years. Approximately three-quarters of patients had a history of prior systemic therapy for psoriasis or UV phototherapy, including UVB. If we only include patients who did not have UVB only, then 60 percent of patients overall were classified as having a history of systemic therapy.

The mean baseline PASI score was 19. The mean percentage of body surface area affected by psoriasis was 28. 93 percent of patients were classified as moderate to very severe by the static physician's global assessment. The two treatment groups, as we can see, were comparable with regard to baseline disease severity.

Treatment effect, that is, the difference between efalizumab and placebo, by PASI 75 was 22 percent in this study. The treatment effect by the secondary endpoints, including static physician's global assessment, of minimal or clear and PASI 50 supported by the primary endpoint. All differences were statistically significant with a p value of less than .001.

The mean absolute improvement in PASI score

over the 12-week treatment period is summarized here. Efalizumab is in red and placebo in black. In this study, a separation between the two treatment groups was apparent by 4 weeks of therapy.

Treatment effect was present in subgroups defined by gender, age, baseline PASI score, and a history of systemic therapy.

The distribution of the percent change in PASI from baseline to the end of treatment is shown here. A positive change here represents improvement. The placebo group is represented in blue and the efalizumab group in red. On the y axis is the number of patients. Due to 2 to 1 randomization, there is roughly twice as much red area as there is blue. Overall, though, we can see that there was an overall shift towards improvement in the efalizumab-treated patients as compared to control. In addition from this graph, we can see that a small number of patients in both groups worsened during treatment.

Here we see the summary of treatment effect, the difference between efalizumab and placebo and efficacy across the four studies. As we have said, these studies had similar efficacy endpoints, patient populations and dosing regimens. Treatment effect, as measured by PASI 75 at the end of the first 12-week treatment period, was reproducible and ranged from 17 to 37 percent for the four

studies shown. The secondary endpoints were also supportive of the PASI 75 across the studies.

Next, let's consider study 2058 in which retreatment was evaluated in a placebo-controlled fashion. The simplified schema for study 2058 is shown here and although this study has several treatment arms, we are primarily interested in that highlighted here in yellow for this discussion.

In study 2058, PASI 75 responders at day 84 were observed until relapse. Relapse was defined as a loss of 50 percent of improvement achieved during the first 12 weeks of therapy. The observation period was variable but could be as long as 6 months. Upon relapse, patients were re-randomized to efalizumab, shown here, or placebo at one of two doses, 1 milligram per kilogram or 2 milligram per kilogram. These patients are referred to as the RT-A group.

The RT-A group consisted of 82 patients who were randomized to retreatment and their disposition is shown here. The first column represents patients who received placebo during the first 12-week treatment period and the second two columns are those patients who received two consecutive 12-week periods of efalizumab. Most of the patients who were re-randomized to receive efalizumab completed retreatment, as we can see here, while fewer than

one-third of those who were re-randomized to placebo completed the retreatment period. Most of these patients discontinued due to non-response to retreatment and entered the open-label extension study 2062.

The efficacy results at the end of the 12-week retreatment period are shown here. Now, these are expressed as a change from the initial treatment baseline or day 0 of the first 12-week treatment period. Among patients who received retreatment with efalizumab, 31 percent of the combined efalizumab group responded at the PASI 75 level at the end of the retreatment period. Also, the majority of patients receiving efalizumab, 67 percent, responded at the PASI 50 level. This is in contrast to patients re-randomized to placebo who had no PASI 75 responders to retreatment. Of note, the large amount of missing data is due to the discontinuation due to non-response that we've already discussed.

Now, the company has presented retreatment results in stable patients as we have heard. However, we feel that these results should be interpreted with caution as this was an open label study and, in addition, some topical anti-psoriasis medications were allowed in this study.

Next, let us consider long-term continuous treatment. Long-term, that is, 6 months or greater,

continuous treatment was evaluated in a randomized placebo-controlled fashion in studies 2058 and 2059. Study 2059 involved a rigorous assessment of efficacy of extended treatment for responders as well as patients who did not achieve a PASI 75 during the first 12 weeks, and I will present the results of the extended treatment in this study.

This is the study schema for 2059. In 2059, patients were randomized at day 84 to extended treatment based upon the determination of their clinical response at the end of the first treatment period. In contrast to 2058, PASI 75 responders were not observed off of treatment but they were immediately re-randomized to a continuous extended treatment period with placebo and two doses of efalizumab, 2 milligrams per kilogram on alternative weeks and 2 milligrams per kilogram weekly.

Although, like study 2058, the design includes several treatment arms, let me first focus on this treatment arm highlighted in yellow, and I will refer to this as the ET-AR group.

There were 40 patients randomized to placebo and 79 to either the 2 milligrams weekly or every-other-week dose during the extended treatment period. The ability of drug versus placebo to maintain a 75 percent improvement in PASI score during the extended treatment

period is shown here. Approximately 77 percent of responders to the first treatment period maintained a PASI 75 level of response during the second 12 weeks of continuous blinded therapy and this is compared to 20 percent of patients who were re-randomized to extended treatment with placebo.

The proportion of these patients experiencing relapse, again defined as a loss of 50 percent of the improvement achieved during the first 12 weeks of therapy, is shown here. Of the patients who remained on active treatment, 92 percent did not relapse, whereas the majority of patients who received placebo during the extended treatment period or the withdrawal placebo group, 67 percent of those patients experienced relapse.

Next, let us consider the outcome in those patients who did not have at least a 50 percent improvement in PASI score, the non-responders, at the end of the first 12-week treatment period. This group is highlighted in yellow. These patients were re-randomized to efalizumab at 4 milligrams per kilogram per week or placebo. Please note that we have very little safety and efficacy information with the 4 milligram per kilogram per week dose.

Among efalizumab-treated patients who were non-responders to the initial 12-week treatment period, an additional 11 percent over placebo achieved a PASI 75

response at the end of the 12-week extended treatment period. Again, only the 1 milligram per kilogram per week dose is being considered for licensure and these data do not directly address the ability of the 1 milligram per kilogram dose to capture additional responders who were non-responders during the initial treatment period.

The company has also presented to you this morning results on extended treatment, in addition to these results. Again, these were from open-label, uncontrolled studies and therefore we should interpret the results with caution.

To summarize, among treatment responders, extended treatment with efalizumab beyond the initial 12 weeks maintained PASI 75 in 77 percent of patients versus 20 percent of patients who were re-randomized to placebo, and the majority, 67 percent, of responders who were re-randomized to placebo relapsed. In non-responders, treatment with an additional 12 weeks of efalizumab continuously without interruption at the 4 milligram per kilogram per week dose captured an additional 11 percent of PASI 75 responders.

Next, let us turn to the integrated summary of safety. The safety database in psoriasis trials included over 2,700 patients exposed to efalizumab. Approximately 2,400 were treated weekly for 12 weeks, 939 weekly for 24

weeks, and 218 for 1 year. 1,620 patients received efalizumab in the placebo-controlled portion, the first 12 weeks, of the four phase III studies.

Next, let's turn to the safety results.

This slide summarizes deaths in efalizumab-treated patients. There were no deaths in the first 12 weeks of placebo-controlled studies. There were 7 deaths in the safety database. 2 occurred during treatment and 5 following treatment. The causes included metastatic rectal cancer in 1 patient, cardiac causes in 3 patients, accident in 1, cirrhosis in 1, and in 1 patient, the cause was undetermined. None of these were attributed to efalizumab by the investigator or by the sponsor and none were attributed to infection.

Serious infections, that is, those resulting in hospitalization, in the first 12 weeks of the four phase III controlled clinical trials are summarized here. The incidence of serious infections was higher in the efalizumab group, .4 percent, as compared to the placebo group of .1 percent. There were three cases of cellulitis, two cases of gastroenteritis, one case of pneumonia and this patient also became septic, in addition to a second case of pneumonia.

The rate of serious infections in the entire safety database adjusted for exposure is summarized here.

The incidence rate for serious infections per 100 subject years is 1.6 in the efalizumab group and 1.2 in the placebo group with overlapping 95 percent confidence intervals.

Serious infections during the first 12 weeks of the controlled clinical experience included one case of pneumonia, as we have seen in a patient who was a 74-year-old man. This was classified as a severe pneumonia with bilateral pulmonary infiltrates. The pneumonia which occurred 22 days following the fifth dose was preceded by an adverse event of a decrease in absolute neutrophil count from a normal baseline. No follow-up neutrophil counts are available. The patient had received five doses of efalizumab. The dose was held due to urticaria and then again due to the decrease in neutrophil count which was noted 2 weeks following the fifth dose. The event resolved with normal chest x-ray on follow-up.

One opportunistic infection was observed in the entire safety database. A 41-year-old woman developed Legionella pneumonia. The patient had an unremarkable medical history with the exception of a history of tobacco use and was on no concomitant medications. She received a 12-week treatment period with efalizumab at the 2 milligram per kilogram per week dose and soon after she developed the pneumonia. She was hospitalized and required mechanical ventilation but survived.

Malignancies diagnosed during the first 12 weeks of placebo-controlled studies are shown here. The number of malignancies diagnosed during this period are very small and this is consistent with the relatively short 12-week duration of observation. There was no increase noted, however, in the efalizumab group versus placebo.

Malignancies in the entire safety database are summarized here. On the left are malignancies diagnosed in efalizumab-treated patients and on the right are the expected numbers based on external cohorts. The expected incidence derived from the SEER database is age- and sex-adjusted. The unadjusted expected incidence rates were given based upon two other cohorts, external cohorts of moderate to severe psoriasis: the Saskatchewan Health and United Health Care cohort.

These comparator populations included adult patients who had a diagnosis of psoriasis between 1995 and 2000 and received a prescription for systemic anti-psoriasis therapy or had ultraviolet light therapy. In efalizumab-treated patients, there were 8 solid tumors diagnosed. The number was comparable to the expected, based upon these external cohorts, and the 95 percent confidence intervals overlapped. In addition, one melanoma was diagnosed in the efalizumab-treated patients, and again, it was comparable to what might be expected.

Now, 2 patients were diagnosed with lymphoproliferative malignancies in the entire safety database. Both of these patients had tumors which were EBV negative and both occurred in the efalizumab-treated patients. One consisted of nodular sclerosing type Hodgkin's disease in a 37-year-old man. The patient received approximately 5 months of efalizumab and he received a total cumulative dose of 29 milligrams per kilogram.

The second patient was a 57-year-old man who was diagnosed with a B cell lymphoma classified as follicular mixed large and small cell non-Hodgkin's lymphoma, stage 1. This patient had received continuous treatment with efalizumab at 1 milligram per kilogram per week for 2 years.

Now, to turn just briefly to the experience that we have learned from the renal transplant trial of efalizumab, there are three cases of post-transplantation lymphoproliferative disorder in this trial of 38 renal transplant patients, and all three of the cases occurred in patients who received 2 milligram per kilogram per week for 12 weeks. This consisted of 19 patients. One of these resulted in death, judged by the investigator as related to efalizumab, and all of the cases were in patients who were on concomitant triple immunosuppressive therapy.

The number of lymphoproliferative malignancies, shown here, which we discussed is two, is higher than that which was expected based upon the SEER database and lower than that derived from the other reference groups. These results were based upon over 2,200 subject years of observation as of the most recent update, and the 95 percent confidence intervals, as we can see, are overlapping.

In the entire safety database, the number of non-melanoma skin cancers, shown here, 20, was higher than the gender- and age-adjusted incidence from the two external reference groups, the Saskatchewan Health and United Health Care, and the 95 percent confidence intervals were not overlapping. There is no SEER comparison for non-melanoma skin cancer as this database does not collect information on the non-melanoma skin cancer.

The comparison to placebo, which I haven't shown here, was limited by the small numbers of non-melanoma skin cancers diagnosed in the placebo group and that was two. These data suggest the possibility of an increased incidence in non-melanoma skin cancer in efalizumab-treated patients. However, the comparator was a non-randomized external cohort. Therefore, we cannot exclude the possibility of ascertainment by us and we cannot draw definitive conclusions from these data.

19 patients, consisting of .7 percent of the entire safety database, experienced serious psoriasis flares. 17 of these patients were hospitalized for psoriasis. Serious psoriasis flares occurred during treatment but were more common upon treatment discontinuation.

This table summarizes the adverse events of psoriasis, both serious and non-serious, during the first 12-week treatment period in placebo-controlled studies. As we can see, there was a higher rate of psoriasis adverse events in the efalizumab group overall as compared to placebo, 3.2 percent versus 1.4 percent. In this comparison, all of the cases of erythroderma and pustular psoriasis occurred in efalizumab-treated patients.

In the entire safety database, there were 15 cases of arthritis which were classified as serious and accounted for .6 percent of the efalizumab-treated patients, and here again, serious typically means resulting in hospitalization. In one case I noted, there was a patient who had other inflammation-associated findings. For example, peripheral edema, fever and a positive ANA. None of the arthritis serious adverse events occurred during the first 12 weeks of placebo-controlled trials.

Overall, arthritis-related adverse events, including all severities, took place in 2.8 percent of

efalizumab-treated patients and 2.2 percent in the placebo during the first 12 weeks of the controlled period. The severe arthritis adverse events in the first 12 weeks of the controlled period were .6 percent in the efalizumab group and .3 percent in the placebo group, and none of these severe arthritis events were classified as serious, as we have already said.

Also, in the entire safety database, there were other rare but serious inflammation-related, potentially autoimmune-mediated adverse events observed. These included interstitial pneumonitis in 2 patients, a serum sickness-like reaction in 1 patient, transverse myelitis in 1 patient, and idiopathic hepatitis in 1 patient.

Thrombocytopenia was another unexpected observation. In the entire safety database, 8 patients were identified with platelets of less than 52,000. 2 of the 8 patients had a platelet nadir of less than 10,000. 5 of these patients were hospitalized and thus were classified as having serious adverse events. Of the remaining 3 patients, 1 patient was identified retrospectively and was diagnosed with prostate cancer and 1 patient had preexisting idiopathic thrombocytopenic purpura.

The characteristics of these 8 patients are highlighted here. They ranged in age from 29 to 71 years.

They consisted of four men and four women and concomitant medical conditions, as we have said, included preexisting ITP in 1 patient, 2 patients had Grave's disease.

Next, I will describe the treatment and outcomes of the 5 patients who had serious adverse events of thrombocytopenia. All 5 of the patients were treated with systemic steroids. Bone marrow biopsies done in 2 patients yielded normocellular results. The events included a 41-year-old woman with a platelet nadir of 10,000. The patient experienced heavy genitourinary bleeding and was found to be antiplatelet antibody-positive. We have received a preliminary update on her condition, that she now no longer requires prednisone to maintain her platelet counts, that initially she received treatment with prednisone.

Another patient was a 73-year-old woman who had a platelet nadir of 3,000. Initially, it was required that her prednisone be increased to control her thrombocytopenia, but subsequently the prednisone dose was able to be decreased. The event is ongoing, and as of a verbal report, the patient was on 5 milligrams per kilogram per day of prednisone. The other patients are reported to have resolved thrombocytopenia.

This slide summarizes the common adverse events with efalizumab treatment that were seen in 3 percent or

higher in the efalizumab group versus placebo and these included headache, chills, flu syndrome, pain, fever, nausea, and myalgia. These adverse events were observed primarily with the initial doses and became less common thereafter.

Next, I'll describe the laboratory changes that have been observed with efalizumab treatment. I will focus on the results seen with the to-be-marketed efalizumab. However, there were no substantial differences observed with the Xoma-manufactured product.

The effect of efalizumab on white blood cell counts is summarized here. Mean white blood cell counts increased by 30 to 40 percent from baseline. Mean lymphocyte counts doubled. The mean eosinophil counts increased by 50 percent, and there was a slight increase in neutrophil counts. Again, the significance of these changes is not understood. They may result from demargination from altered trafficking or other mechanisms.

In the chemistry panel was observed an increase in the mean alkaline phosphatase in efalizumab-treated patients compared to placebo. The mean change in alkaline phosphatase was just over 5 units in the efalizumab group compared to negligible changes in placebo. The highest observed change was 243 units in a patient who received the 1 milligram per kilogram per week dose. There was a

suggestion of a dose effect in patients who received the 2 milligram per kilogram dose, demonstrating a higher change than those who received the 1 milligram per kilogram dose.

In addition to the mean change in alkaline phosphatase, shifts to high post-baseline values in patients with normal or below-normal values were observed in 4 percent of efalizumab patients versus .5 percent in placebo. Both liver and intestinal isoenzymes were shown to be affected, and again the clinical significance of these changes are not understood.

This summary represents the proportion of patients with a shift from low or normal baseline to above the upper limit of normal at the end of the 12-week treatment period on one or more liver function tests shown here. The number of subjects with shifts of one or more liver function tests was higher in the efalizumab group compared to placebo. No patients had shifts for four or five of the liver function tests.

The effects of efalizumab on markers of inflammation are summarized here. Examination of changes in representative acute phase reactants and complement activation products demonstrated some changes in efalizumab-treated patients. In study 2600, the mean levels of C-reactive protein and fibrinogen increased more in the efalizumab-treated group compared with placebo.

Shifts to elevated levels of C-reactive protein and fibrinogen were observed at rates approximately 10 percent higher in patients receiving efalizumab compared to placebo. Adverse events of thrombocythemia were observed in a small number of patients and appeared to be reactive in etiology. The clinical significance of these changes again are not understood.

Changes in C-reactive protein by treatment group are summarized here. Efalizumab-treated patients experienced a mean change in C-reactive protein of .4 versus negligible change in placebo. The maximum observed change in an efalizumab-treated patient was 22 as compared with 6.6 in placebo. The clinical significance again is not clear.

The results of anti-efalizumab antibody testing is summarized here. 6.3 percent of 1,063 patients who had post-washout samples were tested positive for anti-efalizumab antibodies. The median exposure to efalizumab was 167 days. Of the anti-efalizumab antibody-positive patients, 20 percent achieved a PASI 75 and 53 percent achieved a PASI 50, consistent with the overall response rate.

So next, to conclude, treatment response by PASI 75 ranged from 17 to 37 percent, by PASI 50, 36 percent to 46 percent, and by static physician's global

assessment, the range was 16 to 29 percent. Median time to response in PASI 75 responders was 2 months and the median duration of response was 67 days.

With extended treatment beyond the initial 12-were course, PASI 75 was maintained in 77 percent of responders who were re-randomized to efalizumab versus 20 percent re-randomized to placebo. Efalizumab shows relatively limited ability to capture PASI 75 response upon relapse. 31 percent responded with retreatment upon relapse. There were no deaths in the controlled portions of the clinical trials and no deaths were linked causally to the use of efalizumab in psoriasis trials.

The data on malignancies are summarized here. Solid tumors and melanoma in efalizumab-treated patients were comparable to external cohorts. However, larger numbers of patients followed for longer durations are needed to fully assess this. Lymphoproliferative malignancies were higher than expected based on the SEER database but lower compared to other databases, and the number was 2 in all. Non-melanoma skin cancer was higher than expected, based upon the external cohorts and this could possibly be due to ascertainment bias. Overall, no firm conclusions can be drawn regarding the risk of malignancies with efalizumab.

With regard to serious infections, a higher

proportion of efalizumab-treated patients during the initial 12-week treatment period of the controlled trials, .4 percent experienced a serious infection versus .1 percent of control. In the entire safety database, there was one opportunistic infection, Legionella pneumonia, observed, and there was one serious infection, pneumonia, associated with new onset decrease in absolute neutrophil count.

With regard to psoriasis adverse events, there were serious uncommon adverse events of psoriasis which included psoriatic erythroderma and pustular psoriasis, and these resulted in hospitalization in 17 patients.

Rare inflammatory or possibly autoimmune adverse events occurred, including transverse myelitis, interstitial pneumonitis, idiopathic hepatitis, and a serum sickness-like reaction. Thrombocytopenia consisting of platelets of less than 52,000 occurred in 8 efalizumab-treated patients and resulted in hospitalization in 5 patients.

Laboratory changes seen with efalizumab included elevations in total white blood cell counts, lymphocytes, and eosinophils. There was a mean elevation in alkaline phosphatase and a higher rate of shifts to above normal in several liver function tests. In addition, there was an increase in acute phase reactants. All are of

unclear clinical significance.

Finally, potential areas for further study that will be the topic of our discussion this afternoon include the use of efalizumab as an intermittent versus a long-term continuous treatment, the long-term monitoring of immune function using clinical and laboratory assessments, large-scale long-term studies to assess risk of infection, neoplasms, and other adverse events, and safety and efficacy in children.

Thank you for your attention.

DR. STERN: Thank you very much. The panel has questions? Lynn?

DR. DRAKE: Dr. Papadopoulos, on the non-melanoma skin cancer, did you in any way separate out patients who had had previous light therapy for their disease? Because most of the patients enrolled in the study had had previous therapy of some sort. Were you able to distinguish between patients who had had previous light therapy which might predispose them to developing skin cancer versus those that did not have any previous light therapy?

DR. PAPADOPOULOS: No. I don't have a specific analysis distinguishing the two subgroups. The external cohorts which were used as comparison had similar exposures, previous exposures to light therapy and systemic

psoriasis treatments.

DR. DRAKE: Thank you.

DR. BLAUVELT: In the four phase III studies, you talk about the results being similar, but it seems like 17 and 37 percent are very different to me. So is the 37 percent study the outlier here? What's your opinion on that?

DR. PAPADOPOULOS: That's my opinion. That one was the highest one. It seemed to me to be the outlier.

DR. MARZELLA: If I may comment, the confidence intervals around those estimates overlapped.

DR. KATZ: Dr. Papadopoulos, concerning the thrombocytopenia, the patient with the prostate cancer, was that metastatic?

DR. PAPADOPOULOS: That's the same question that I have. I'm interested in knowing what the tumor burden was, whether it involved bone marrow.

DR. KATZ: That would be crucial.

DR. PAPADOPOULOS: I think that should be a question for them.

DR. KATZ: Then the other question concerning the same thing. The Grave's -- I speak out of ignorance now because I didn't look that up -- but I wasn't aware that that would be any predisposing to thrombocytopenia.

DR. PAPADOPOULOS: Well, that was an

observation that I had, and I'm not fully aware of the literature with regard to other autoimmune diseases and any possible predisposition towards this type of finding.

DR. KATZ: The point being, if the prostatic was not metastatic and there's no good literature on Grave's associated, then those preexisting conditions would be not relevant.

DR. PAPADOPOULOS: It may or may not be and that's not really my area of expertise.

DR. STERN: Could I just remind everyone to speak into the mike, please?

Did you have a comment, Warwick?

DR. MORISON: The comment I was going to make is the connection is probably through ITP which is an autoimmune disturbance as is Grave's. So they have increased frequency, I presume.

DR. STERN: Dr. Tan?

DR. TAN: Yes. I have two questions. At what time points are the lab data collected? At baseline and at 12 weeks for the white blood cell counts and lymphocytes?

DR. PAPADOPOULOS: The white blood cell counts were collected at baseline, and in most of the studies, they were collected day 56 and at day 84, and in one study, in study 2600, we have data at baseline and day 84. It could possibly have some bearing of the onset of

thrombocytopenia observed, most of the cases of thrombocytopenia observed after the 3-month initial treatment period.

DR. TAN: The reason I asked for that is other correlative studies were done about the laboratory data versus the clinical endpoints.

DR. PAPADOPOULOS: I'm not aware of any correlation between the laboratory and clinical endpoints.

DR. STERN: Dr. Plott?

DR. TAN: Just one more. This is related to the response, the treatment effect. So we have heard that in the four trials, there is not much difference in terms of -- they can be pooled, in one word. So I'm curious. What is the response rate if you pool these four trials together in terms of, for example, like a meta-analysis? What is the true response rate in PASI 75, for example?

DR. PAPADOPOULOS: I'm not sure I have that information.

DR. STERN: Do you mean the cumulative response rate?

DR. TAN: If you pool all the data from these four trials together, what is the response rate?

DR. STERN: At 12 or 24 weeks?

DR. TAN: Both.

DR. STERN: I think at 12 weeks, you could pool

that and my recollection is that the difference between placebo for three of the trials was right around 18 to 20. In one, it was about 30, and they were about equal size. So it's probably about 23 or 24 percent at 12 weeks.

My understanding -- and correct me if I'm wrong but I think it's an important point -- is we have no way of really deciding on the basis of placebo-controlled information what the true at 1 milligram per kilogram response rate is in any trial at 24 weeks because the only one where there was maintenance of placebo control was initially -- I've forgotten whether it was 1 to 2 milligrams followed by the 4 milligram dosage, where there was in fact always a comparator group. We have a variety of observational information on longer than 12 weeks but no placebo control data.

DR. TAN: So we should know what is the real response rate at 12 weeks?

DR. STERN: I'm sorry?

DR. TAN: So we should know what is the 12-month response rate in terms of PASI 75?

DR. STERN: What is the pooled PASI response rate?

DR. PAPADOPOULOS: I don't have the specific calculation.

DR. TAN: These four studies do vary.

DR. WALTON: There is some variation between the studies as has been noted, and although we tend not to rely upon meta-analyses where we can avoid it for a whole variety of reasons, if one conceptually pooled them, then as Dr. Stern noted, you'd wind up with a PASI 75 for the 1 milligram dose of somewhere on the order of 23-25 percent. One might think about, if one is doing that, whether the conclusion of 2 milligrams is the same as 1 milligram influences whether you pool that or not. There's lots of different ways to do post hoc pooling and because of that, we tend not to rely on it, but we think that if you did that, you'd obviously wind up with a number that is essentially right in the middle of the four different studies.

DR. PLOTT: My question had to do with safety in the case of opportunistic infections and the one in particular with Legionella. There's mention in the briefing book about other cases that were involved there.

Can you explain maybe a little bit about that particular case? Because the mechanism of action of the drug gives us concern for opportunistic infections. Was this a case that was among several other cases where there was a documented outbreak or can you tell us a little bit about it?

DR. PAPADOPOULOS: My understanding is that

there was a cluster of cases of Legionella and there were other patients admitted to the same hospital. Now, again this is a little bit out of my area of expertise, but we would still call this an opportunistic infection because it doesn't really occur normally in patients who are not somehow compromised, either advanced age or some other cause.

DR. STERN: Dr. Epps?

DR. EPPS: Just a quick question. There was an earlier adverse event with requiring audiology testing. Was that not seen with the Genentech product?

DR. PAPADOPOULOS: The bottom line of the audiology results showed that there was no ototoxicity of the drug and that was done in an earlier study. In the Genentech studies, the ones that evaluated the Genentech product, it was not done. It was done in the earlier 2058 which was exclusively a Xoma study.

DR. EPPS: And what is your opinion on the missing data?

DR. PAPADOPOULOS: I'm sorry?

DR. EPPS: I guess it was about 24 percent in one particular area was missing. Do you remember that part?

DR. PAPADOPOULOS: Are you referring to the retreatment? Are you referring to one of my slides?

DR. EPPS: Yes.

DR. PAPADOPOULOS: One moment, please.

DR. WEISS: Dr. Epps, was this some of the slides with the retreatment, where there's extensive amounts of missing information, a small data set to begin with and then small amounts of missing data?

DR. PLOTT: You're looking at slide number 27, aren't you?

DR. PAPADOPOULOS: Yes. Thank you. Slide number 27. So this slide shows the missing data which this refers specifically to retreatment, not to the first 12 weeks, and patients who initially received efalizumab and then were reclassified as responders after the first 12-week treatment period and then who were re-randomized to placebo or active drug, this shows a subset of that particular subset. What we see is that patients who initially received efalizumab and received placebo in retreatment upon relapse, there was a large amount of missing data, and this was due to treatment discontinuation due to non-response. So as you can imagine, they were relapsing. They got placebo. They did not get better, so they discontinued. So that's what accounts for the large amount of missing data there.

DR. STERN: However, when you look at your percentages in the efalizumab column, they add up to well

more than 100 because in fact the denominator, which I think is what you used, is well more than 55 patients. It's on the order of the high 60s. So the percentages should absolutely be reduced by about 20 percent in terms of the outcomes.

DR. PAPADOPOULOS: Are you referring to the PASI?

DR. STERN: Right.

DR. PAPADOPOULOS: The greater than PASI 50 actually includes this group here. So that's exactly right, yes.

DR. STERN: Dr. Blauvelt?

DR. BLAUVELT: I was curious to see a few serious adverse events to arthritis, but I didn't hear at all today, either from the company or from you, any data on the effects of this drug on concomitant psoriatic arthritis in the study population, whether any of that data was captured or at least symptoms of psoriatic arthritis captured. I just am curious to know if it has any effect on concomitant psoriatic arthritis.

DR. PAPADOPOULOS: The adverse events of arthritis included psoriatic arthritis, and several of the patients who had serious adverse events had an inflammatory arthritis. So those were included.

DR. BLAUVELT: But there must be a much larger

database or at least symptoms of psoriatic arthritis that were captured. Did it have any effect, positive or negative, on arthralgias or symptoms of psoriatic arthritis?

DR. PAPADOPOULOS: There were acute adverse events of arthralgias, and actually the drug is being studied now for psoriatic arthritis.

DR. MARZELLA: I think that question should be directed to the company, if they would like to address it.

DR. JOHNSON: Yes. We didn't formally collect information on efficacy in arthritis in these trials. Our colleagues at Xoma are, in fact, conducting a formal randomized placebo-controlled trial in psoriatic arthritic patients, looking at the outcome of their arthritis. That study is actually fully recruited but not completed as yet.

DR. STERN: Dr. Ringel?

DR. RINGEL: I apologize for making this a multi-part question, but it all concerns autoantibodies. The first question is in the patients who had thrombocytopenia, one of them did have antiplatelet antibodies. Number one, when you said one did, did that mean that the others did not or were they simply not tested? That's the first part.

DR. PAPADOPOULOS: My recollection, to my knowledge, is that only 1 patient was tested and that we

don't have full information, and the company would probably want to address this further, but from my knowledge, there was 1 patient who was tested and that patient was positive.

DR. STERN: Does the sponsor have any more definitive data on that group?

DR. JOHNSON: I'd like to ask Dr. Warkentin to discuss that issue, if it's possible. He has reviewed the cases in some detail.

DR. STERN: Could we just have at this point the proportion who were tested and the proportion who were positive?

DR. JOHNSON: Yes. Can you supply that answer? I think it's also important to understand the antibody that we're testing for is antiplatelet versus antidrug antibodies.

DR. WARKENTIN: My name is Ted Warkentin. I'm a hematologist at McMaster University and I have a clinical and research interest in platelet-antibody interactions, platelet-drug interactions.

One patient was tested for antiplatelet antibodies and they were positive. I should point out that the routine test, so-called platelet associated IgG, that's performed in a number of laboratories is actually not a good test for drug-induced thrombocytopenia. That's a common misunderstanding. That's the test the physicians

ordered.

So part of my role in consulting with the company has been to say and to advise that going forward, if additional cases arise in the future, that there should be a protocol in place to do very specific platelet antibody testing to try to understand better the relationship of that situation.

I should also point out that anti-Raptiva antibodies were tested as part of this study, and there was no link between those antibodies and developing any thrombocytopenia. There's no linkage there at all, to just clear that up.

DR. STERN: Thank you. Dr. Ringel?

DR. RINGEL: That was pretty much the second part of the question. There was one other piece to that in terms of anti-Raptiva antibodies. In one of the tables in the backgrounder that we received, hypersensitivity reactions were more common, 18 percent versus 6.7 percent, in the placebo, and I'm wondering if there were any other clinical correlations between anti-efalizumab antibodies and any clinical findings, either laboratory or symptomatic.

DR. PAPADOPOULOS: There is data on that from small numbers of patients that I received, in particular with regard to arthritis adverse events, that possibly

suggested, again not statistically significant but a possible suggestion that on patients who were positive for antibody had a higher rate of arthritic adverse events. So we just need to interpret it with caution because it was from a small amount of patients, small numbers.

DR. STERN: Any specific data from the company on that question?

DR. JOHNSON: Thank you for the opportunity to respond. Yes, we would agree with Dr. Papadopoulos' conclusion.

I think one important comment we'd like to make is that the few events that she highlighted in her presentation, the transverse myelitis and those cases, in none of those cases -- my recollection is correct, I think -- did they have antidrug antibodies.

DR. STERN: Are there any other questions by the committee?

(No response.)

DR. STERN: I have one question before the break, which is, as an immunosuppressive drug, could someone please explain to me why we have a doubling of lymphocyte counts and 20 or 25 percent of the people having increases in C-reactive protein? Not being an immunologist, that's a little bit contrary, especially since these were done fairly far out and just demargination

would seem to not be a persistent one. Jim, if you have an answer for that, I would really appreciate it because it confused my simple mind.

DR. KRUEGER: There was perhaps a little bit of confusion that was placed this morning in the description of LFA-1 on leukocytes, and at least one of the things I want to do is clarify that there is some selectivity here for T cells versus other classes of leukocytes because that goes to your question of why lymphocytosis.

You heard that there are in fact three different beta 2 integrins that are widely talked about, LFA-1, MAC-1, and this molecule called the third leukocyte, integrin.

Well, it turns out that T cells mainly have LFA-1 on them and about a third or so of T cells have alternative expression or additional expression of this MAC-1. Now, in contrast, macrophages, neutrophils, and B cells have relatively higher and more consistent expression of these other integrins.

So the prediction going into this is that if you block LFA-1, the T cell effect is going to predominate and because this is what allows T cells to adhere to inflamed endothelium, you would expect that demargination and possibly some other retrafficking causes would selectively let T cells be increased.

In reality, if one goes to blood counts and measures what happens in the different leukocyte populations -- this is administration of active drug over a 12-week period -- you see not much change happening in neutrophils over this treatment period, not much change happening in monocytes, but there is this lymphocytosis that's going on which doesn't break it down into T cells and non-T cells. But I've done that at the peak of this reaction here and have categorized cells into CD3 positive lymphocytes which are T cells here versus other types of lymphocytes which are B cells and NK cells, and you can see that in reality then, the prediction holds that it's really a lymphocyte-selective effect.

T cells are about 70 percent of lymphocytes and then lymphocytes are only 50 percent or so or 30 percent of -- that's why you get this 20 percent increase in overall leukocytosis, but it's almost all a T cell signal that's going on. Does that help you?

DR. STERN: That helps me but confuses me. The things I think about when T cells go up, it's either you're making more, you're destroying less, and the demargination is usually a relatively temporary phenomenon, that homeostasis reasserts itself over a long period of time, over 12 weeks. So I'm confused.

DR. KRUEGER: So I've actually looked at

adherent cells to endothelium and plaques, and you have to realize that the number of cells that are in plaques are an order of magnitude higher than the number of lymphocytes that are in the circulation, and if you look, say, out at about 8 weeks, you see almost no adherent leukocytes on inflamed endothelium in psoriatic plaques or the resolving plaques versus the baseline where there are many, many adherent cells. So I think demargination counts.

The increase in lymphocytes here is mainly in memory cells. That would be the cells that would be trafficking into the inflammatory sites. There is a small increase in naive cells and so there may be some disruption of lymph nodes circulation trafficking going on and that may be cumulative over time, but I think on the most part, we are affecting the trafficking patterns of memory cells which includes their entry into psoriatic lesions.

DR. STERN: That's very helpful. Thank you.

DR. BLAUVELT: While you're up there, another immunology-related question.

DR. KRUEGER: The C-reactive protein for me is one that's a little bit harder, and I think it probably is related to the other end of the molecule, and that is, to the Fc portion of the molecule bridging with monocytes and leading to some release of TNF and IL-6, which has been demonstrated certainly at early phases in treatment, and

then to the induction of acute inflammatory protein, such as C-reactive protein, maybe even in hepatocytes, by the small cytokine signal that would be chronically generated with that. But that's speculative. I can't prove it, but I think there's enough in the biology here that would let you get away with postulating an explanation.

DR. BLAUVELT: Well, I was going to ask with antibodies bound to lymphocytes, why is it not lymphocyte-depleting? Why isn't that binding complement and depleting the lymphocytes that have bound antibody?

DR. KRUEGER: I don't know.

DR. JOHNSON: I actually got a question over Dr. Krueger which is not bad.

(Laughter.)

DR. JOHNSON: The molecule is actually constructed that the backbone is actually not a complement-fixing antibody.

DR. STERN: Do we have a final question before we break for lunch?

(No response.)

DR. STERN: If not, we'll break for lunch, resume promptly at 1:00. Thank you.

(Whereupon, at 12:00 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:01 p.m.)

DR. STERN: Good afternoon. We're about to enter the open public meeting, and I am required to read something which I've never read before and the emphasis is the Commissioner of the FDA's, it's not mine.

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 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 sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have 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 guess that's a new regulation.

We'll now open the open public speaking and we have a total of five speakers, three of whom signed up well in advance and will be allotted 10 minutes, and two of whom have signed up since the period and will be allotted 5 minutes each. Let me read their names and if there's anyone else who would like to come forward, it's not too late since there are a few minutes allotted to the open public session that are available.

The people we have on for this afternoon in the order they'll appear are: Ms. Holsinger, Mr. Lemelin, Ms. Pevnick, Mr. Newcomb, and Ms. Harris. Is there anyone else who would like to add their name to the roster?

(No response.)

DR. STERN: If not, we'll begin with the 10-minute presentation by Ms. Holsinger.

DR. HOLSINGER: Thank you for the introduction. Ladies and gentlemen, I'm delighted to be here and I can start with saying that I am paying my travel expenses to this meeting and the National Psoriasis Foundation has paid for the travel expenses of two of our members who are here to speak to you today. So I am delighted and honored to be able to be here.

My name is Leslie Holsinger, and I'm the

Chairman of the Board of Trustees of the National Psoriasis Foundation, and I'm here today on behalf of the foundation and the community it represents to support approval for Raptiva.

Psoriasis has severely impacted my life. I've had psoriasis for 20 years, since I was 18 years old, and I developed psoriatic arthritis when I was 29, and psoriasis is no stranger to my family. My father has psoriasis, his only sibling, my aunt, has psoriasis, and his father, my grandfather, had psoriasis as well. By sharing my story, I hope that the FDA will better understand the urgency felt in the psoriasis community for more treatment options.

The National Psoriasis Foundation was established in 1968 by a grassroots network of people with psoriasis and psoriatic arthritis. They were volunteers, both patients and physicians, and the same kinds of people govern the foundation today. The foundation's mission is to improve the quality of life of people who have psoriasis and psoriatic arthritis, and through education and advocacy, we promote awareness and understanding of the disease, ensure access to treatment, and support research that we hope will eventually lead to effective management and ultimately a cure.

Financial support for the foundation comes every year from our almost 50,000 individual members and

also from nearly 20 biopharmaceutical companies, and this support does include that from Genentech as well as its competitors. However, at the same time, the Psoriasis Foundation is solely responsible for all of our programs' development, content, and delivery.

So we are here today on behalf of the patient-driven organization that directly affects half a million people annually by providing advocacy, medical education, support groups, conferences, publications, and a website. We also work on behalf of more than 5 million people in the United States with psoriasis and psoriatic arthritis. So we are their voice as well.

We've all seen psoriasis, but I want to emphasize how physically disabling and emotionally disabling the disease can be, that it's not just a cosmetic problem. With this slide and the next one, whether large body surface areas are covered with psoriasis or, as in this slide, smaller surface areas that can be severely impacted, psoriasis can be very painful, debilitating, and is very visible. It's a very serious disease.

The foundation's national survey research has shown that 1.5 million adults in the United States suffer from moderate to severe psoriasis, and of those people that are affected with moderate to severe psoriasis, 75 percent of them say that it has a moderate to large impact on their

every-day life, 26 percent of them say that it alters their daily activities, and 21 percent of them say it actually stops their daily activities.

It causes trouble with sleep in 36 percent of the people with moderate to severe psoriasis, affects clothing choices. It can profoundly impact one's work, family and personal relationships. I know. My psoriasis, which is very visible to everyone who sees me immediately, and is also very painful, keeps me awake at night in pain, dramatically affects my choice of work, how I play, my relationships with other people, and how I care for my family.

The Psoriasis Foundation believes that there is a need for more treatment options for people with moderate to severe disease. Why? Because psoriasis is not just a cosmetic disease but rather a lifelong serious disease. Our research has shown that 78 percent of people with moderate to severe psoriasis do not use currently aggressive therapies because of concerns about side effects and effectiveness. So 78 percent of this population of people would categorize themselves as being undertreated, and patients make choices, often difficult choices, about safety, cost, effectiveness, complexity, and usability of various therapies. I can tell you personally finding the right therapy that works for you at various times in your

life in a lifelong battle with chronic disease is incredibly challenging. So having choices is really important.

On a personal note, most of the therapies that I have used over the years have not worked great, as I would categorize them, or they have worked for a while and then stopped working. I've used methotrexate on and off for 8 years and have found this and other systemic therapies that I have used to have side effects that are very difficult to tolerate.

Also, I found treating my disease and planning for a family to be very difficult. Most of the available treatments are currently not compatible with a pregnancy. Starting a family is complex. It not only involves the time pregnant, but in fact involves significant time prior to being pregnant. So it's a very difficult problem for people of my age. Raptiva and other directed therapies like it may offer more hope and are very welcome as needed options for women and men during these years of starting their families where options are sorely lacking.

The Psoriasis Foundation believes that new therapies, like Raptiva, may offer new hope and options for physicians and patients. It has the potential to control psoriasis and improve quality of life, and importantly, it may be a fit for individual patients better than some

existing therapies.

So, in summary, moderate to severe psoriasis can dramatically affect the quality of one's life which you'll hear more about from our next two speakers. People with psoriasis need and deserve more therapy options and access to new therapies like Raptiva is important and desirable.

So let me introduce the next two speakers. Mark and Robin are both members of the National Psoriasis Foundation who have actually used Raptiva, and they're here because they want to share their stories about Raptiva and what a difference it has made for them.

On a final personal note, with three generations in my family affected by psoriasis, I know that my son Jeremy, who is 22 months old, he has a good chance of developing psoriasis. I'm here today because I want Jeremy and his generation to have choices for the future.

Thank you for the opportunity to speak with you.

MR. LEMELIN: Good afternoon. My name is Mark Lemelin. I should probably also state that other than the connection through the NPF, I do not have any financial ties to any other form of this presentation.

I want to thank you for giving me the opportunity today to come and speak to you about my

experiences with various treatments and why it is that I am so enthusiastically in support of Raptiva.

In March of 1977, I was 19 years old, when some mysterious red patches first appeared on my scalp. I went to a dermatologist and was diagnosed with psoriasis. Now 26 years later, I've come to learn and understand a great deal about this disease and the emotional and physical toll that it exacts.

Within 18 months of that initial diagnosis, my psoriasis had spread throughout the entire body. As my condition spread, the discomfort associated with it grew steadily more severe.

The emotional costs of the disease began to appear at this time as well. Early on, I made a decision that I was not going to let psoriasis control my lifestyle or my social or recreational habits. Of course, there were some adjustments that had to be made. It's simply not possible to be totally unaffected emotionally by such a disorder. I even had to plan my very day around treating of my skin.

Swimming, which had been a favorite pastime of mine, proved to be very irritating to my skin, so I very rarely got the opportunity to swim. Socially, I decided that there was really very little that I could do about other people's perceptions of me or my condition. The

important thing to me was to not think of myself as a victim and not to portray that image to others.

I also discovered that there are a number of environmental factors that can play a role in the progression of the disease. Factors such as diet, stress, and climate can all have harmful or even beneficial results. For instance, there are certain times of the year that I can expect a flare-up to occur simply because of the seasonal changes.

As for stress, my own personal experience is that there is not a direct link between a high stress level and a worsening of my psoriasis. In fact, personally, I tend to see the link between the two as being the opposite of what the conventional wisdom would have you think of it. In other words, to me, psoriasis itself causes stress. The burden of living with an unstable chronic condition is stressful in and of itself. Additionally, when I'm not in remission, there is never a single waking moment that my sensory system is not completely overloaded with itching, burning, stinging pain from literally hundreds of sources all at the very same time.

As much as one can try to function normally, there are times where there is really very little emotional energy left over to deal with just the regular normal demands of life. Knowing that I'm not always able to

function fully and be there to provide what I should causes additional stress and loss of self-esteem. So in a very real sense, psoriasis has affected my entire family, my business, and my social network.

As the condition worsened, medical treatments grew to include corticosteroids, ranging in strength from mild to super-potent, Dovonex, Protopic, anthralin, urea, salicylic acid, coal tar, PUVA, UVB, oral prednisone, hydrocortisone injections, retinoids, and methotrexate. Non-prescription choices included an array of lotions, moisturizers, shampoos, and supplements.

While each therapy has had varying levels of success and different side effects, there are some generalities that can be made.

First, no one therapy works the same each time it's tried. A treatment that has been very successful in the past may not work as well the second time around.

Second, compliance can be a very real concern. Many treatments require two or even three doses a day to be most effective. That can be extremely difficult to do, especially when a topical treatment may take an hour or longer to complete.

Third, each one has its own form of side effects, ranging from mild nausea and dryness to more serious side effects, such as elevated blood pressure and

impaired liver function. I had to be taken off of retinoids due to a sudden and significant elevation in my cholesterol levels, for instance. Those of us who are of childbearing age have some very real concerns, as was mentioned earlier, with a number of treatments.

Fourth, every treatment that I've ever tried has eventually lost its effectiveness. Over time, the body seems to build up defenses against that particular treatment. So as a result, rotating therapies is necessary to stay a step ahead of the body's defense system.

Lastly and probably most significantly, no treatment has ever totally cleared my psoriasis, and so it's against that background that my search for a safe, effective, long-term option continued.

I received a very timely notice in the mail from the National Psoriasis Foundation about a study in my area. I had just completed topical and UVB treatments and my skin was not responding to either one. My psoriasis was about as bad as it had ever been, and the overall discomfort level had reached extreme levels. Clearly, I needed some sort of a systemic treatment, but I was reluctant to go back to either retinoids or methotrexate because of their long-term effects. I considered talking to my doctor about cyclosporine, but I was concerned with some of what I had read about it. I called to get more

information on this study. So after reading the information on the drug, I made the decision to proceed.

Compared with every other treatment that I have tried, nothing has been easier or more convenient to administer. I meet with the research nurse every month and with the study doctor once every three months. At each meeting, objective measurements are made. In addition, subjective information is gathered to measure the changes in my personal comfort.

Now, while the initial results, after the initial 12-week phase, showed that I would have been considered a non-responder, in other words, having less than a 50 percent PASI score improvement, the current objective scientific data shows an improvement of over 90 percent. My own personal subjective sense is that the improvement is even far greater.

At the beginning of the study, psoriasis covered 45 to 50 percent of my total skin area. Currently, it covers a total of less than 1 percent. There's no indication that my clearing has reached a plateau and I continue to see and feel improvements. Tolerance of the drug has been excellent. I may be a bit more likely to catch common bugs that run through the house and the office than I was before, but I would say that that just simply makes my immunity system more normal.

The positive impact on my lifestyle cannot be overstated. I've gained one to two hours of personal time every single day, time that I used to spend treating and moisturizing my skin. Now I have more personal time with my wife and six children. The quality of that time has also been enhanced. Freed from the stress and the discomfort of my condition, I am now more fully involved and fully engaged in everything I do.

So, to summarize my experience with Raptiva, no other treatment has matched the improvement in my psoriasis. No other treatment has had as positive an effect on my personal comfort and my emotional well-being. No other treatment has provided so low a level of negative side effects. No other treatment comes close to making full compliance in administering the drug so easy, and no other treatment offers as long of a potential remission period.

Certainly ongoing research is needed to ensure safety of the long-term use of Raptiva. However, the more safe and effective choices there are, the better the prospects for long-term results. Those of us who are affected by this chronic disorder hope that you will recommend the drug's approval, thus providing us with one more quality option.

Thank you.

MS. PEVNICK: I was going to start off by taking off my jacket to show you that I'm so comfortable about my skin right now, but it's too cold.

(Laughter.)

MS. PEVNICK: But I do notice that as you look around, there's so many people with dark-colored clothes and it's no big deal, but for me to be able to wear a black jacket is a very monumental event because for over 20-plus years, my wardrobe consisted mostly of white colors.

First of all, I'd like to thank Dr. Stern for inviting me to speak to you today. I'd also like to thank the National Psoriasis Foundation for bringing me here.

My name is Robin Pevnick and I'm from St. Louis, Missouri, and I've been affected with this horrible disease for about 28 years and my success with the miracle drug now known as Raptiva.

I first noticed I had psoriasis at the formidable age of 16. Having a dad with the disease, I was well aware of the horrible effects that psoriasis had on me and my father. I remember constantly wiping flakes off my shirts, looking around to see if anybody noticed that they were there. As a teenager, shopping is a big part of your life, but for me, it was terrifying. I would go with my friends and wouldn't even go in the dressing room with them because I didn't want them to see the flakes falling onto

the floor.

Bathing suits were the worst item to buy because I had to look for bathing suits with shorts or with the highest back with the least amount of skin showing, and when I went to the pool, which wasn't often, I'd wear a cover-up and I'd only take it off right before I'd get in the water and then I'd only be in the water from head up because I didn't want anybody to see my skin

Getting up from chairs and beds and walking all left behind flakes which would be constant reminders of where I'd been.

I believe I went into teaching partly because children don't usually judge you the way adults do. I could respond to a child, oh, it's just poison ivy, but if I told an adult that, they would question that and look at me like I was some sort of freak of nature or something similarly bad. I also grew up very uncomfortable about my body in general and therefore this created a problem when I started dating. I didn't want to tell boyfriends or anybody that I had the disease or I wouldn't show them my body. Even when I eventually got married, I dressed in the dark. I wouldn't even show him and he made me feel so comfortable, but this disease makes you feel such a low self-esteem. It was a very major part of my life.

My mom took me to see a lot of doctors, growing

up, to try to help me. She knew how bad this disease made me feel about myself and how much it lowered my self-esteem. My dad felt even worse because he felt it was his fault. The visits to these doctors proved very unsuccessful and humiliating. I felt like I was a guinea pig on display for the physicians who would bring in other physicians to the office to look at my body.

I know I've been on every topical medicine out there. The doctors then tried putting me in the hospital for tar and light treatments. The greasy tar was smelly and it ruined any clothes that it came in contact with, not to mention it was ineffective. I then did PUVA treatments which caused my body to break out in freckles which I still have today. It was also inconvenient to work in these treatments three times a week and have a job. My husband decided to put a light treatment box, ultraviolet light box in my house. The results were minimal and the burning hurtful.

One doctor decided to put me on methotrexate. I was nervous about the side effects and the long-term effects of liver damage. I was also too afraid to stay on it for more than three months and I didn't see much improvement.

Frustrating years and years passed and the only treatments I found were pounds and pounds of ointments. I

stopped going to doctors because I felt like nothing was helping.

One day, my best friend called me and told me about a study she heard on the radio for patients with severe psoriasis. Not believing anything would help, I didn't even want to go to the doctor's office. My friend told me it was a pain study and that I'd have nothing to lose. And I had never heard of Dr. Leonardi before and I was extremely reluctant. However, I was curious.

After going to his office and seeing all the forms and the risks that could be involved, I went home thinking there's no way I'm going to try this study. The office called me back and convinced me to discuss it further, saying I would be a perfect candidate. They told me how I'd be monitored so closely that they would catch any signs of significant effects. This drug is now known as Raptiva. They told me it was a once-a-week injection which was very easy for me. I honestly tried this drug thinking I wouldn't get any results because nothing ever did.

After two short weeks, my skin started responding incredibly. My psoriasis was disappearing before my very eyes. I can truly say it was a miracle drug. Aside from a couple of headaches at the beginning, it was extremely easy. Sorry. I'm a very emotional

person.

After 12 weeks, I finished the study and I was completely, completely cleared. The first time in 28 years. There was not even a residue of where my psoriasis was and I felt beautiful. My daughter was having a bat mitzvah and I didn't have to buy a long-sleeved dress to wear at the bat mitzvah at the end of April. I could wear a sleeveless dress and feel beautiful and very comfortable.

Even after I completed the study, my skin stayed clear for well over two months and I was so happy. The psoriasis began coming back and I was able to get on another study. This time, there was no hesitation on my part to get back on it. My only disappointment was I had to stop this drug when the trial was over. I couldn't believe I was not able to continue a drug that was a miracle-worker for me. Dr. Leonardi told me it needed to be FDA-approved and then I could get back on the drug.

At its worst, what did my body look like at its worst? It was painful to even walk. Clothes on my body hurt. My skin was a bright red mass of cracks, bleeding and flakes. I would take daily oatmeal baths for some relief and I would then cautiously put on the ointment and lotion on my body to try to soothe the area. Even the applications of these treatments were painful to me. You want to wear short sleeves for comfort because clothes hurt

you so bad, but you don't want other people to see your red scales all over your body and ask you questions. I wouldn't want anybody to feel that kind of pain.

That's me. We lost it. So that was probably good.

Now you can understand why I felt it was very important to come here today. There's a terrific need for new therapies that make sense. I am a mother of two. When I was pregnant, I had nightmares that my child would be born covered with psoriasis. I wouldn't even ask my doctor if that could be possible because I was afraid of his response. It was a long nine months.

Because my dad has the disease, I am fearful my children will. Knowing that there are drugs such as Raptiva out there, I am to some degree at ease. I don't want my children to suffer the anguish, the bleeding, and suffering that I've had all these years. I urge you for all psoriasis patients around the world to make this treatment available.

Thank you.

(Applause.)

DR. STERN: Our next presenter is Mr. Lyle Newcomb who has been allotted 5 minutes.

MR. NEWCOMB: Thank you. I'd like to thank Malia Tee from Bass and Howes for inviting me to come. I

was able to catch a red-eye last night and get in here this morning. I am very happy that I'm able to talk to you folks this morning about psoriasis.

I have been a sufferer of psoriasis since my mid-20s. I am in my 60s.

Psoriasis is a debilitating disease. My heart goes out to these folks. I sit back there wanting to shed tears watching and listening to what they had to say. I've gone through the same things for years. There were no drugs out there that would take effect. I've tried the tar baths. I've tried all the ointments. I've tried the foams. I've tried everything.

Like the first gentleman, I'm a very strong-minded man and I thought, I'm going to beat this. I'm not going to let psoriasis affect me and change how I do or conduct my life. That did not take place. Over the years, I withdrew. I started wearing long-sleeved shirts. I no longer wore shorts in public. I was ashamed of the scales and stuff that were on my legs that were scratching and bleeding all the time, on my elbows itching, on my sides, on my knees, on my head, on my face. I can only tell you and echo all the things that have been said here today.

1997, I read an article in the newspaper that said come to the Oregon Research Center in Beaverton, Oregon. Dr. Miller, Dr. Mathison were the doctors, and

they were giving out and testing different drugs for psoriasis. I tried for four years, through all the different drugs that they had with no success. I still had psoriasis. It was getting to the point I didn't think there was ever going to be anything that would work for me.

Dr. Miller came to me and says, I have this new drug. He did not give me a name of it. He says, I have this new drug. It's going to be a shot that we'll be giving you. I'd like you to try it. He says, you will not be on anything except the real drug. We'll try it for three months and then, if it works, we'll go to a maintenance dose.

That happened in March of 2001. Just like the young lady Robin, within a month's time, my 30 percent of the body that was covered with psoriasis was clean. I had no psoriasis. Less than a month and a half. Within a month and a half.

I'm fortunate. I am still on the study. That study, to my knowledge, will end in March of this coming year. I will have finished three years with it. I'm here to tell you I need this drug. There is no cure for psoriasis at this time. This is the only thing, and to steal a line from the National Psoriasis Foundation, it works for me, it works for these folks. I know it's going to work for other people out there. They need this, so

that we can lead normal lives.

To let you know how important this is, in 1993, I was diagnosed with diabetes. I am the type II and I control it as best as I can, but you know that diabetes people don't heal well, and it takes longer for them, if they're cut or if they get some kind of a bruise, to regain that without being ill. Raptiva has not given me any ill side effects whatsoever, and I heal faster than I did prior.

I want to thank the makers of the Raptiva for doing that. I call myself, because everybody knows that psoriasis is an unsightly and ugly sight, I call myself ugly-free now.

Thank you.

(Applause.)

MS. PROTHRO-HARRIS: Good afternoon. My name is Kadesta Prothro-Harris. I thank the committee for allowing me to speak. I was not assisted by Genentech at all. Bass is the company that has helped me to get here because I did need assistance. I'm 49 years old. I'm married. I've been married for six years, the second time, and I have four biological children, five stepchildren and a brand-new adopted daughter.

My children think it's significant for me. I developed psoriasis in 1991 at 37 years old. At that time,

before actually seeing the psoriasis, having another child was very important to me. I had a tubal ligation, so for me it was going to be in vitro or something else major like that. With psoriasis, it took over my life. So at that point, I put off trying to get pregnant. Then I ended up getting remarried later on.

I had topical creams, prednisone. I had antibiotics, Benadryl, Valium. They did that because I had a major outbreak and a reaction, so the Benadryl and the Valium was to slow everything down. I went into UVB.

Actually for me, it took 18 months to almost 2 years before they actually diagnosed it as psoriasis. I was in an HMO. I was being treated by a general practitioner. So that was the treatment that I was receiving.

After about 18 months, when I reached the point that the plaque covered so much of my body and became infected, they then sent me to a dermatologist who diagnosed it with biopsy and started me on UVB. UVB was successful two times where I was able to clear up. Then after stopping, the plaque came back. I would clear up again.

The decision was to put me on methotrexate. For me, that was a major decision because still in the back of my mind, I'm going to have another child, and because

nothing else at that time was working, I did go ahead and go onto the methotrexate. For me, my female trouble happened that I started having 20-day cycles and became anemic while on methotrexate. The only thing they could attribute it to is something in there was reacting with me. So they took me of. I am still anemic. That didn't change. So methotrexate is not an option for me in the future. Went back onto UVB because there was nothing else. We didn't want to risk anything else, so UVB was all that there was. That just simply didn't work for me.

I was able to go onto Raptiva. I, like the other people who presented today, the first week, all of the itching, all of the burning, all of the pain went away. It changed my life because then I could sleep all night. It was wonderful. My attitude got better. My children decided that I was probably the meanest person in the world for a very, very long time because you are uncomfortable. When you don't sleep, all of the things going on, things change.

My youngest son is 16, and I developed psoriasis when he was 4. Being on Raptiva when he saw me change, the pain go away for the first time in his recognition or recollection, I became pleasant on a consistent basis. So now that I've been off of it and I have started the plaque coming back and the attitude is

changing a little bit, he has begged me to please go back on it, and I beg you to find a way, please, to make this happen for us.

I did go off in 2002, in March. I did remain plaque-free for 5 months. Plaque started coming back. I was able to use topicals and I responded there with topicals, up until January of this year. For me, stress has a lot to do with my psoriasis, and we got word that we were going to be able to adopt a newborn and with the stress of that, it started coming back, and so I definitely need Raptiva in my life.

Also for me -- I didn't hear this reflected with anyone else -- I was not able to work. I was a dispatcher for the Vallejo Police Department, and one of the things that happened in being on the medication and having the itching and things like that that I was going through, I was taking Atarax which impairs your judgment and you cannot be a 911 dispatcher with impaired judgment. You run the risk of the city as well as yourself personally being sued. Because we couldn't control my medication or control what was going on in my life any other way, I was put on disability. At that time, I was a single parent with four children and literally changed my life, how I could live, what I could afford to do. I had the support of my family, so we were able to survive, and I

appreciate that.

But if I would have had Raptiva in my life at that time, I would probably still be working and had a sizeable retirement because the job was a good job. It was an excellent job. I would have liked to have stayed there, but I didn't have an option, and I would like to see for other people for them to have the option, and especially for childbearing people, I would love to see them have the option of going on a medication that clears out of your system when you stop taking it after a short period of time comparatively to what happened with methotrexate where we waited two to three years, and they have an opportunity before it's too late. I'm 49. My chances are basically over. But at 42 years old, when I went on methotrexate, if I had gone on Raptiva, I would have had a little more time. But fortunately adoption is available and I was fortunate enough to have a little girl because of that.

So I do thank you and I again from my son Richard at 16, myself, my family, we ask you to please, please approve this medication. Thank you.

(Applause.)

DR. STERN: If there are no further speakers to come forward, we'll conclude the open public portion of this meeting and go on to general discussion.

For the rest of the afternoon, we will have two

tasks. One is for general issues and concerns and then, as you all know, there are, shall we say, a quite comprehensive and lengthy list of questions put to the committee by the FDA which, beginning no later than 3 o'clock, and if the general questions end before, whenever that is, we will use the rest of the afternoon to go through those questions.

I would ask the committee members to sort of review those questions, and if they have questions that are particularly pertinent to the individual questions put forward by the FDA, it might be most efficient to raise those at the time we're discussing the FDA questions, and so for the next moments up to an hour and 20 minutes, we'd like to talk about general conceptual issues that are really not covered in the FDA questions.

Lynn?

DR. DRAKE: Dr. Stern, thanks. This has nothing to do with what you just said. I just wanted to take a moment to thank all the volunteers who came forward with their personal stories. I think it takes a great deal of courage to come up and talk about your life and show pictures of yourself and talk about your babies. I just want to thank you because I think it helps keep what we're doing in perspective, and so I want to compliment you on your courage and again thank you for coming forward.

DR. KATZ: I just wasn't familiar with Bass, and two of the presenters said that they came through Bass and not Genentech. What is Bass? I'm not familiar with that. Is there some connection between that and -- what is that company? Is that a drug company?

MS. PROTHRO-HARRIS: It's Bass and Howes and they're an advocacy for patients organization.

DR. KATZ: It's a patient advocacy?

MS. PROTHRO-HARRIS: Yes.

DR. KATZ: And is that supported by drug companies or where does it get its support? I mean some of us are not familiar with this company that is sponsoring some of the speakers. Does anybody know? Is it patient advocacy? Is it a national company? Does anybody know anything about this? I mean, we're told Psoriasis Foundation has support from the drug companies, but I want to know what that company is.

MR. NEWCOMB: I can't tell you whether or not they do. Malia Tee of Bass and Howes called me up and asked me if I would like to go talk to the National Psoriasis Foundation and see whether I could make arrangements to come and be here today. Unfortunately, my schedule didn't work with their schedule and they had some other things.

DR. KATZ: No. I just want to know what the

company is.

MR. NEWCOMB: I don't know, sir. She just called me up and invited me.

DR. KATZ: Who supports the company?

DR. STERN: I've been informed by the executive secretary that it's in the record who the support was, and unless the sponsor would like to tell us from their end if they have any relationship, it's really a moot point and that's completely up to the sponsor and it's just in the record.

DR. KATZ: Well, it's not a moot point because each one of us around the table has to declare conflict of interest, and if any speaker from the floor bears some conflict of interest, we should know.

MS. STUTTS: Hi. My name is Mary Stutts, and I'm the head of Corporate Relations at Genentech, and Bass and Howes is a patient advocacy organization and they do receive funding from different drug companies, including Genentech.

DR. KATZ: Thank you.

DR. STERN: General questions? Yes?

MS. KNUDSON: Dr. Stern, I would like to know whether there's been any profile that's emerged to determine which patients might be responders and which might not.

DR. STERN: What a wonderful question. I think probably that's really a question directed to the company; that is, based on your studies, can you tell us who's most likely to respond?

DR. JOHNSON: Yes. Certainly we try to look at that in the studies, and first of all, I think it's important to note that there are no biological markers that we can detect at this stage which predict response. The response that we see in terms of biological markers, if you give people this drug, you block CD11a, there's a disconnect between those who will respond and those who do not respond.

We did analyses based on the subgroup analyses of categories of patients at baseline and looked very carefully at that. So if you could show me that slide, please.

So if we take this slide and what this slide represents is a slightly different way of showing the data, but basically what we're showing here is the treatment effect in the pivotal study 2390, and so instead of seeing the 27-percent effect here, what you're seeing is the treatment effect which is the active drug minus the placebo drug shown as a point estimate with confidence intervals around it. This is an aggregate analysis of all the studies. So this is about 27 percent minus 4 which is 23

percent.

If you look at baseline characteristics, such as the baseline PASI score, previous exposure to systemic therapies or duration of psoriasis, there are really no indicators of a particular group of patients that are able to respond. So having shown you that data, I'm afraid the answer to the question is no, there's no particular profile clinically of a patient who is more likely to respond to this drug than anybody else.

DR. STERN: I believe the FDA addressed those points as well and certainly all the data from the clinician's perspective unfortunately does not direct us within the groups to who is more likely than others to respond.

DR. WALTON: Yes. Within the patients studied.

DR. STERN: Within the patient population studied.

DR. WALTON: We were not able to identify any particular factors that would distinguish.

DR. STERN: Dr. Morison?

DR. MORISON: Yes. I had a question which I guess I'm directing towards the company, and that is, I have no experience of testing quality of life in a routine fashion, only a lot of experience in seeing patients with psoriasis, and I was rather astonished that the mean

quality of life score was 11.

Then I looked up how you assessed the score which is a series of 10 questions, and that means that the mean quality of life score was a little bit disturbed for each of the 10 questions which sort of astonished me in a group of patients who are classified as moderate to severe psoriasis. I was wondering whether someone who's got experience in measuring quality of life was also surprised with that.

DR. JOHNSON: To respond to Dr. Morison's question, I think that I personally don't have a huge amount of experience testing quality of life in patients, but the instrument that we've used has been well validated and looked at with other interventions, and the changes that you see are pretty much across the board. So in the slide that Dr. Kaiser showed you in the core presentation, I think that was the point that he was trying to get across, that if you look at patients with changes in each domain, you see a large proportion of the people who are treated compared to their baseline score have dramatic responses. So this is significant changes from a lot or very much to very minimal changes at this stage.

I can also show you an alternate slide which looks across all of the patients at the proportion of patients in each group who had a 2-point change, a 10-point

change, and so like that, if that would be helpful.

DR. MORISON: Probably I'm not expressing myself very well. What surprised me is here we've got a group of patients who are being labeled as moderate to severe psoriasis, which is the sort of psoriasis that I deal with, and I wouldn't have thought any of my patients would have answered a little bit upset by any of those questions.

Now, you're familiar with that questions are. It's 10 questions. Does it interfere with your daily life and such like. I would have thought patients with moderate to severe psoriasis would have said they're markedly disturbed, as the patients who have been speaking to us this afternoon are obviously markedly disturbed by having a lot of psoriasis.

DR. JOHNSON: Right.

DR. MORISON: That's one point of the question.

The second point of the question is to go from 11 to a mean of 6 wasn't very dramatic to me in terms of changing their quality of life if we're truly having a vast effect on psoriasis. So I guess what I'm saying is if someone can explain that to me. I'm just wondering whether these patients really are moderate to severe psoriasis as such.

DR. JOHNSON: I think predominantly the effect

on the mean value overall is diluted out by the people who clearly didn't respond. So if you look at it in this context, if I may be permitted to show this slide, if you look at the proportion of patients in the placebo group and the Raptiva group -- and we've plotted here the absolute point changes in DLQI improvement from the baseline category -- you'll see that there's 30 percent of patients here who have 10 or greater than 10 improvement. This column would include those people who had basically a score of 0 or no impairment of quality of life for that stage.

So if you look at the distribution of these things, it's consistent across each of those distributions and clearly those patients with a PASI 75 or greater would be clustered up at this end of the curve. So I think it's the difference between looking at the mean value overall for the patient group versus the responses in individual groups of patients.

I'm afraid I can't explain to you the point why the baseline value is 12 out of 30. Lee?

DR. KAISER: Let me just address this in a certain way. When you look at the range of the DLQI, it goes from 0 to 30 and the baseline was about 12, so just above a third. Body surface area, 0 to 100 obviously, the mean baseline was just below 30 percent. So relatively speaking, it's fairly consistent. PASI goes 0 to 72. The

mean baseline was around 20. So in a way, the DLQI is a little higher than that.

Now, I agree you can't just say these scales are linear, but in a sense, these patients have a DLQI baseline comparable to these PASI and body surface area.

DR. STERN: I'm sorry, but that makes no sense to me as an explanation, and having done a little bit with DLQI, the idea behind DLQI is exactly the dichotomous nature of a disease like this as we've heard about from a variety of people between extent of disease, not reflecting the true burden of the disease, depending on the person's social situation, extent, the location of disease on the body, and all those other factors. So trying to look at how much the disease interferes with their daily life satisfaction and functioning and that in fact is not analogous to percentage.

I would not expect it to be highly correlated in a way that you've sort of described, and I would say if we take your reasoning forward, my first conclusion would be you've given us further emphasis that the kind of patients you've treated -- this is not what I believe -- but the logic of yours is that the kind of patients you treated aren't very bothered because, as Dr. Morison says, they only have a little bit bothered on all these dimensions when in fact objectively and what we've heard

from patients, a large proportion of these patients are clinically affected and apparently are also substantially bothered by it.

I think there are a variety of problems with the DLQI that make it very complex to look at, particularly as an aggregate, and I think if you go back to your first slide of explanation, I think you can see that there are a couple of dimensions that in fact there were fairly high proportions of individuals, particularly symptoms, embarrassment and clothes, where there were more than 50 percent of the individuals who rated these a lot or very much, and in fact, I would bet if you looked at your mean reduction, most of that comes from improvement in these particular domains.

Whether this is a good scale that weights all of these domains equally, that's a topic for another discussion. I think it's to me interesting that it's these three domains, two of which I would put very high weight and one of which, because I'm a terrible dresser, I would put lower weight on, but that's my own personal values. So I think it's very complicated and interesting, but I don't think we should say, oh, it's a third of this, a third of this, and a third of this, and they're all co-correlated.

I see Dr. Menter nodding his head.

DR. MENTER: The issue related to DLQI and the

degree of psoriasis, moderate to severe, certainly is a very vexed one. Dr. Lebwohl, Dr. Caro, and myself have just completed a 480-plus patient study in which we actually took 50 aspects of quality of life and tried to relate it by PASI scores and the three of us did PASI scores on each one of our patients. This is actually in press at the present time. And 12 key points related to quality of life were statistically significant, and I hope that this will be some way to get around the weighting that is not present currently in the DLQI.

Thank you.

DR. STERN: I'm sorry for the digression but we're going to continue in order. Dr. Ringel?

DR. RINGEL: You can go to someone else next.

DR. STERN: Dr. Blauvelt?

DR. BLAUVELT: Are there any animal data in chronic suppression of CD11a and whether the mice, for instance, would be susceptible to infection or cancer?

DR. WEIR: I'm Andrea Weir, toxicologist with FDA, and I've been reviewing the Raptiva submission.

The company conducted one study in mice, and the antibody that they used to conduct this study was an antibody that's known as MUM-17, and it's analogous to efalizumab, except it's specific for the mouse CD11a.

In this study the sponsor conducted -- it was a

general toxicology study -- in the high-dose group which is 30 times the clinical dose, the animals were treated weekly just as it's to be used clinically. There was one mouse that developed some infections, but with just one mouse, you really can't say anything and so really no real weight can be put to that. There was certainly no evidence of any systemic infections that were seen in the number of the animals.

This study was a 6-month duration study and because it was just a 6-month duration study, it's difficult. You can't really make any firm statement about the carcinogenic potential of the MUM-17 because of the duration of the study.

DR. BLAUVELT: But 6 months in mice is equivalent to about 20 to 30 years in humans. So that's pretty good.

DR. WEIR: But typically for mice, unless they are genetically-modified mouse, typically for a mouse in the study that's designed to study carcinogenic potential, it's usually an 18-to-24-month study. So if you see something, tumors forming, and in a 6-month study like this was, that certainly would raise considerable concern, but not seeing anything, it's difficult to give it much weight.

DR. BLAUVELT: So these are just baseline. They weren't challenged with infectious organisms to see

whether they were more susceptible. It was just looking to see if they spontaneously became infected with something or were they challenged with organisms and shown to respond as well as untreated mice?

DR. WEIR: They were not challenged.

DR. STERN: Two hands from the company about that issue -- or three hands. I'm sorry.

(Laughter.)

DR. JOHNSON: I apologize. I mean, we completely agree with the agency's opinion on this case. I would just like to point out that the model that we used in that experiment was in fact a model that has a tendency to produce lymphoma. It has been published previously that in 6-month studies with cyclosporine, the model that we used has a rate of lymphoma of about 10 to 30 percent, and in fact, in the control group of that model, there was one case of lymphoma. There were no cases of lymphoma over that 6-month period which I agree is a limited exposure, but there were no cases of lymphoma in that particular exposure.

DR. WEIR: With that model, that's not really an accepted model of being sensitive to lymphoma and that was the P53 wild type mouse, and just because there's been two studies done with cyclosporine that showed tumors formed at 6 months, you can't take that and say that that

particular mouse strain is susceptible to the lymphoma. I mean, part of the genetic background of that mouse, the C57 black mouse, is one that's susceptible, but it's recognized that that's something that starts developing at about 15 months of age, whereas the animals in the study that you conducted were sacrificed at 6 months.

DR. STERN: And from your response, let me just get a point of clarification. There were no provocative photocarcinogenesis studies. In this model, we'd like to see what happens when you expose mice first to UVB and then expose them to the mouse equivalent antibody in terms of seeing if there's a difference in tumor load between the controls and those.

Were there any of those studies done? That's obviously, as we've heard from everyone who's testified today, particularly relevant to the large number of patients who have had PUVA and UVB in the past who might be candidates for this drug, should it be approved.

DR. WEIR: No, those studies have not been conducted.

DR. KRUEGER: I just want to provide a little bit of background outside of the animal model that was set up at Genentech, and that is, there have been a few genetically-engineered knockouts of LFA-1 in mice, and in that instance, there have been challenge studies with

infectious organisms of immune function. The response to bacterial antigens is pretty much uniformly intact, and where there is a bit of compromise is that there are certain viral infections where the response is not handled as well as normally but they're handled partially, and things like LCMP, which are not viruses that are clinically relevant in people. The immune deficiency that's indicated is just basically giving the subset of viral responses which would probably be predicted from a higher role of LFA-1 function and CD8 positive T cells and impairing that kind of response.

DR. STERN: The next question from Dr. Schmidt.

DR. SCHMIDT: I have a personal reflection and then two questions. My wife has psoriasis and severe psoriatic arthritis and is on methotrexate, and now at least I know why she's mean to me sometimes. So I appreciate that.

(Laughter.)

DR. SCHMIDT: My first question is nails. Nails is one of the most difficult things in psoriasis that I see, and I'd like to know if there is a response with the nails in this medication.

Then my second question is when people give this to themselves, is this easy, difficult? Is it invasive when you do it? I'd like to have some comment on

that, also.

Thank you very much.

DR. JOHNSON: I wonder if I should just stay up here.

DR. STERN: Actually perhaps if you stayed and if there was someone else from your group who you thought might be better, just call them.

DR. JOHNSON: Okay. Thank you very much.

So, Dr. Schmidt, in response to the second part of your question, a large majority of the patients who have continued with this therapy beyond 12 weeks have, in fact, self-administered, and the reports that we get from patients are that it is relatively easy to do.

To answer your first part of your question regarding the nail disease, we didn't formally collect information on that. So I'd actually ask Dr. Lebwohl or Dr. Menter to comment on whether they had observed any changes in that, but we formally didn't review that.

DR. LEBWOHL: As you know, the time for nails to clear usually lags about 6 months behind skin, and the studies, at least the initial studies, didn't last that long. The patients whom I see regularly -- and again this is very anecdotal because we did not formally follow nails -- are patients who, when they came off, were switched to phototherapy and so I take care of them now, and they've

had an improvement in nails, but they were also getting other treatments afterward.

I believe that with this and with other agents, just as with methotrexate or cyclosporine or Alefacept, once the psoriasis starts to get better, approximately 6 months later, the nails improve as well.

You had a second question as well.

DR. JOHNSON: The self-injection.

DR. LEBWOHL: The self-injection. You teach patients once. It's very easy. I think that patients are surprised at how easy it is.

DR. STERN: Dr. Epps?

DR. EPPS: Thanks.

I don't know whether I have more of a comment or a question, but I know I've focused on some of the people who did not respond, and I think that in a way that's a missed opportunity because the people who don't respond give us a lot of information for a lot of reasons. Did they drop out because it didn't work? Did they drop out because they don't like the needles? Do they drop out because of a mild side effect? What can we do to alleviate that?

The people that were included had greater than 10 percent. Well, it could be 12 percent. There could be 90 percent involvement.

I don't know whether I have a better indication about whether the patterns she alluded to. Does palmo-plantar or not respond? Do certain areas of the body respond better than other areas of the body? We don't have an answer about nails because we just don't have enough follow-up.

As a clinician, I don't know whether I have enough information to know who's a good candidate. Why would I exclude this one? Why would I include this one who has failed this therapy or that therapy?

I think sometimes when we talk about complications and that sort of thing, it's helpful because we can perhaps narrow down those people. The people who did flare, the people who had serious psoriasis complications, 17 out of 19 were hospitalized. People who had thrombocytopenia, 5 out of 8 were hospitalized. I don't think those can be minimized. Those people had real serious complications. If I can avoid that as a clinician, that's very helpful. That comes from you all --

DR. JOHNSON: Right.

DR. EPPS: -- telling us, well, these are the patients who did not do well, these are the patients for whatever reason -- it doesn't necessarily reflect poorly on the medication, it reflects on which patient population may be most helpful or most helped by this medication.

Obviously we're hearing from the choir and that's great, but we want to hear about the ones who need saving. Right?

DR. JOHNSON: Absolutely. I think what I could actually do is ask Dr. Caro to come because he's reviewed those cases that you referred to, those 19 cases, in some detail, and our evaluation of the data -- it's the quality of the data. There's no formal evaluation of these data, but our evaluation of the data, I think as clinicians, allows us to say something about the likelihood of what to do and how to identify those patients. So if I would ask Dr. Caro to just review that for you briefly.

DR. CARO: I'm Ivor Caro, and I'm now a dermatologist at Genentech. However, until 3 months ago, I was a clinical researcher doing studies particularly in psoriasis with many of the biologics, including Raptiva.

When I started at Genentech, I also was interested particularly in the patients who developed serious adverse events of psoriasis, and as has been pointed out in the briefing book, there were 19 such patients. I reviewed, as best I could, all of these cases and this is just a brief summary of the patients.

A couple of important points. More of these occurred when the drug was discontinued. So this rather artificial situation of a clinical trial whereby one treated patients and certainly in the early trials, the

treatment was stopped and no further treatment or very little further treatment could be used for another 12 weeks. The trials were actually modified further along just because of this particular point, that if you stopped this medication abruptly, you may run the risk of a flare of psoriasis, and as you can see in the first line, 14 of the patients had these serious events of psoriasis, predominantly erythrodermic, a few pustular, a few inflammatory plaque forms of psoriasis.

The "no" refers to patients still on treatment and one of those actually should go into the other column. This was a patient who responded, was in the washout phase, psoriasis was recurring, was given one dose of Raptiva, and developed an erythrodermic psoriasis. So I would class that actually as occurring in the washout. So in my mind, that's 15 after Raptiva treatment, 4 on treatment.

What I noticed was it was much more common in the patients who did not respond. So from my perspective as a recent clinician, if my patient is not getting better with any treatment after 8 to 12 weeks, particularly if that patient is getting worse, my advice, both to the patient and to my colleagues, would be to transition that patient to another therapy, not stop the therapy and wait to see what happens.

Then finally, of some interest was that more of

the adverse events of psoriasis, these erythrodermic flares and a few patients with pustular psoriasis, 11 versus 8, occurred at the higher dose levels, the 2 milligrams or the 4 milligrams, as compared to the 1 milligram dose level.

DR. STERN: Dr. Drake?

DR. DRAKE: While we're shifting gears back to quality of life, I had a question about that. I've done a little bit of work in quality of life, and it impresses me that the only study you used in this was the index. Did you use any SPFs or the PBWs? Did you use any other quality of life forms or measures in coming up with this particular data set?

DR. JOHNSON: The only other patient subjective response was an itch criteria which we looked at, change in itch from baseline to week 12.

DR. DRAKE: Well, then what I would say is I think we shouldn't get too hung up on the DLQI because, as you pointed out, Rob -- I don't want to use the word superficial, but it's kind of a screening tool. It's not a real quality of life measure and it's not disease-specific. I mean it's very useful in that it gives you a trend or a notion of what might be occurring, but it's not disease-specific and it doesn't measure the general health of the individual. It doesn't begin to address the total burden of the disease.

The DLQI doesn't do anything about costs or out-of-pocket expenses, for example. Just one glaring hole. I mean, it doesn't begin to address the whole issue of quality of life. It's a useful tool in my opinion to screen, but it's not disease-specific.

However, having said that, if you look at the trends on baseline on the DLQI on this, the responses to the 10 specific areas that Warwick mentioned are fairly consistent with other studies we've seen that look at quality of life or DLQI in the realm of psoriasis. So I think it's consistent, and therefore I would say that one could potentially make the observation then that the improvement or the change in the DLQI is probably reasonably on target as a measure of a trend, but I don't believe it's an absolute measure of quality of life. It's certainly not a measure of the burden of the disease.

DR. STERN: Dr. Plott?

DR. PLOTT: My question had to do with dose selection. We mainly talked about 1 milligram and 2 milligram and that going up doesn't provide additional benefit. What about lower doses? I wonder if you could just address that.

DR. JOHNSON: I can address it unofficially. The data that we have on that, I'm not sure has been completely submitted to the agency there, but we do have a

study where we're looking at tapering the dose. So after 24 weeks of treatment, we've reduced the dose effectively to half a milligram a week, and although the large proportion of patients do maintain their response at that dose -- I'd have to check and show you the data, if that's okay with the FDA, since you haven't seen this data yet.

DR. WALTON: Yes. I think you've qualified that as being something we're not familiar with. So we really can't discuss it in detail, but I think it's something of interest to the committee.

DR. JOHNSON: The taper regimen effectively is .5 milligram a week, and so if you look at the PASI response over this period in the .5 milligram, you see a loss of that response generally from 43 percent to 36 percent, not huge, but it does suggest that when we look at other studies of longer-term follow-up where we see a maintenance of that 45 percent response, there is a slight drop in efficacy when you drop the dose to .5 milligram. If we drop the dose to .5 milligram, we would probably still saturate and block the majority of CD11a in most patients but not every patient.

DR. STERN: I'm sorry. Could you define the denominator here? Are the 232 the individuals who reached PASI 75?

DR. JOHNSON: No. 232 would be the number of

patients who entered into the study. So who entered into the taper period of the study.

DR. STERN: So the PASI responses, the continuance of PASI 75 -- what are we seeing here? That's where, I'm sorry, I'm being data-dense.

DR. JOHNSON: Sorry. The numbers get confused here. The 2390 study was a 12-week study. At the end of that study, both the placebo and the active group, both went on to active treatment, and the people at the end of a further 12 weeks -- so at the end of 24 weeks of study -- went into randomization of either receiving 2 milligrams every other week or 1 milligram every other week. I think that's right. Sorry. 1 every other week or .5 a week. So effectively the same dose.

So at the end of the 2391 period, 43 percent of the original patients had achieved a 75 percent PASI and overall 74 percent had achieved a PASI 50. If you follow that cohort around in an intent-to-treat manner, that's the response you see.

DR. STERN: Just so I understand this, this is saying at the end of essentially the open trial, the 2391, the second 12 weeks were an open treatment trial. This was the distribution of response among individuals: 43 percent judged to be PASI 75, and 74 percent in total a PASI of 50 or better?

DR. JOHNSON: Yes.

DR. STERN: 6 weeks later, at half the dose essentially administered in one of two schedules, either lower dose every week or intermittent dose, that had been reduced to 58 percent overall and 36 percent PASI 75 for about 20 percent of individuals essentially who had made PASI better than 50, still being there, about 80 percent were that way 6 weeks later.

DR. JOHNSON: That's our interpretation of the data. In other words, if you're going to continue with therapy, don't drop the dose to half.

DR. STERN: What confused me is I thought this was going to be an argument that lower dose worked and you're saying what I conclude, that if 20 percent of people lose substantial benefit in 6 weeks, you probably don't want to wait for 16 weeks.

DR. JOHNSON: No. We would absolutely agree with that.

DR. KRUEGER: There are some additional data that are published from phase II studies where different doses were administered IV and then the saturation of LFA-1 on cells in blood versus T cells in tissue was looked at, and it was clear from that that .3 mgs per kg, which is about equivalent to .5 subQ, gave you reasonable but not fully complete saturation in tissue, but if you doubled

that dose, the saturation was much better, as was down regulation of LFA-1. So if you take the rough equivalence of IV and subQ, I think that argues that we're looking at what's probably about the minimal dose that's going to be producing consistent saturation effects in tissue.

DR. JOHNSON: Thanks, Dr. Krueger.

DR. STERN: I'll resist the temptation to ask a question; instead, stay in order. Dr. Sawada?

DR. SAWADA: It's my understanding the company is looking for continuous use application of this medication for patients. I was wondering if they would give us an idea or the clinician idea of what parameters are we going to be following on patients who are on continuous application of this medication.

DR. JOHNSON: I think our assumption was that that would be based on the clinical response and the discussion between the patient as to whether the drug is working for the patient.

DR. SAWADA: This is assuming that the medication is working, and I know we're going to be looking for petechiae and this sort of thing, but is there any sort of blood work or regular check-up that you guys are recommending for following?

DR. JOHNSON: No, we're not anticipating any monitoring at this stage.

DR. STERN: Dr. Ringel?

DR. RINGEL: I want to get back to the issue of subgroups again. For cyclosporine, when the indication was given for psoriasis, the company was pretty much advertising it for psoriasis in crisis. What I was wondering was that I recognize that Raptiva was used in patients with stable psoriasis, but in study 2058, when patients were discontinued after 12 weeks and then started to flare, when they restarted Raptiva, only 31 percent of them achieved a PASI 75.

So what I'm wondering is does anyone feel that there's sufficient data to say that unstable or flaring psoriasis does not respond well? Perhaps that's the subgroup that we can tease out of this or, in other words, that Raptiva is for psoriasis not in crisis. I don't know how you would state it, but is there enough data or perhaps feeling from the clinicians who use this that perhaps people who are flaring would not be a good candidate?

DR. JOHNSON: I'm not sure. Was that question addressed to me?

DR. WALTON: I think we've already presented the totality of the data we have available which was exactly the information that you referred to.

DR. RINGEL: Do you feel that there's enough data from that one study to say that, or is that really

just trying to tease too much out of it?

DR. WALTON: I think that is very interesting data but it's a very limited amount of data, but nonetheless, it's very important to recognize that that data is present.

DR. LEBWOHL: One thing that you can say is that patients who stopped efalizumab and then flare have a low likelihood of achieving a PASI 75 and that's clear from the data. I think that what we didn't know when we first started doing this study is that patients would flare when you discontinue it, and I think that a message that we got from this study is that this has to be for long-term use. In fact, I think it's very important, if this is approved, that the label has to say you can't cavalierly discontinue this drug. You have to be prepared to replace it with something else. Very much like methotrexate, where you wouldn't just take somebody on 15 milligrams a week and go to 0 the next week and keep it that way for months, I think it's very important that patients be transitioned to other therapies so that you remove that instability in psoriasis that was observed.

The other, I won't say, flaw in the way the study was done but the way the study where we were allowed to retreat patients was done was even if the psoriasis was coming back quickly, we had to wait for 50 percent relapse

in order to institute systemic therapy, and I think going forward, in practice, you would not do that. If you see psoriasis coming back quickly, you'd jump in with another therapy. You wouldn't wait to reinstitute therapy until it was 50 percent worse. So that's, I think, an important message that should be learned from that study.

DR. STERN: Dr. Katz?

DR. KATZ: We saw that very dramatic slide of the patients who went from a score of 50 to 2 and so that's certainly instructive. I assume that you have slides on many of the patients. How many patients do you have of that sort?

DR. JOHNSON: In all of the formal placebo-controlled studies, they were followed with photographs. So we have a very large number of photographs, in the order of 2,000 photographs.

DR. KATZ: Did you tabulate how many are that dramatic?

DR. JOHNSON: Well, the photographs would exactly follow the PASI score. So they would be interpreted as the PASI scores.

DR. KATZ: But PASI 75 was more dramatic than just getting a PASI of 75, would it not be?

DR. JOHNSON: So if it would be helpful, I can tell you the proportion of patients who had a PASI 90

score.

DR. KATZ: Yes.

DR. JOHNSON: Is that what you were looking for?

DR. KATZ: Yes.

DR. STERN: Alternatively, could you tell us how many people in your trials had PASIs above 30, let's say, rather than above 12 and the median of that? Is that partly what you're asking?

DR. KATZ: No. You don't mean PASI of 12.

DR. STERN: No. A PASI of 30 to start, and what proportion of those improved by 90 percent. I guess that would be --

DR. JOHNSON: Oh, I don't know that I have the data of that subset of that subset. I can show you the response in people with higher PASI scores was very similar. In fact, that was the subset analysis that I showed you previously.

DR. STERN: Right. But could you give us the distribution according to initial PASI? It's in your documents. I believe you cut it at less than 16, 16 to something or other, and above 30. So could you give us that distribution and then give us the PASI 90 for the above? So there are 213 individuals.

DR. JOHNSON: So there are 213, yes. And

clearly, the confidence intervals are wider because it's a smaller sample, but the point estimate here is totally consistent with those in the moderate range and those in the lower range.

DR. STERN: So with these data, there were about 50 individuals of the 213 who started out with a PASI absolute number above 30 who reduced their PASIs by 75 percent. Could you give us the comparable 90 percent PASI for the group that started with PASI greater than 30? The 213 most severely affected individuals.

DR. JOHNSON: Not at this time. We can certainly get back to you with that data.

DR. STERN: Okay. But some number less than 50 out of the 213?

DR. JOHNSON: Yes.

DR. STERN: Okay.

DR. JOHNSON: Does that answer your question, Dr. Katz?

DR. KATZ: I really wanted to know in that dramatic improvement that you certainly got with some patients, how many patients got that much dramatic improvement.

DR. JOHNSON: So the best way to show you that probably would be through the PASI 90 scores which, if my backup team could find that slide for me, I can tell you

because I'm afraid I don't know that number off the top of my head. Perhaps I could come back to that while they find that data.

DR. STERN: Dr. Plott is next.

DR. PLOTT: My question had to do with subgroup analysis that you must have done for the agency or the company. Have you identified any particular differences from the general population with regard to the sex, age, and race analysis of subpopulations that may have been done? Anything that's different in one of these subpopulations that's not proved?

DR. WALTON: In terms of efficacy, you're asking?

DR. PLOTT: Well, it might be efficacy is not as strong in one figure or --

DR. WALTON: I wanted to make sure what you were asking.

DR. PLOTT: Right.

DR. WALTON: For all the subset exploratory analyses that we did, to the degree that we're able to, because obviously there are some very small subsets where there simply aren't enough data to draw any conclusions -- there are always going to be that, but within the subset analyses that we are able to do, we really were not able to distinguish any particular factors in which the treatment

effect was notably different between subsets.

DR. STERN: Dr. Morison, then Dr. Tan.

DR. MORISON: I want to revisit the question of who we are going to treat. The patients to be eligible for these studies had to have stable psoriasis unchanged for the previous 3 months, as I understand it or as I remember. That's one point.

The second point is we have visited the question of patients who are flaring or rebounding after a course of treatment, 12-week course of treatment, did not do well and presumably, as Mark has mentioned, Dr. Lebwohl has mentioned, a lot of these patients were probably in a stage of active inflammatory psoriasis.

Taking those two pieces of information together, I would suggest that perhaps a contraindication at this point in time, since we don't have any information to support anything else, is that only patients with stable psoriasis should be treated as part of the labeling.

DR. STERN: Dr. Tan?

DR. TAN: Yes. This is really related to the subset analysis as well, also with Dr. Katz's question. For that slide that was just presented, it seems for patients with a PASI greater than 30 to start with, the response is higher. Is there a subset analysis on that?

DR. WALTON: I think you saw the subset

analysis that Genentech showed and ours is essentially similar. As they pointed out, the confidence interval is broader on that subset because it's a smaller subset. So yes, the point estimate as they showed was --

DR. JOHNSON: I can show that slide again.

DR. WALTON: Okay. The point estimate is slightly higher than for the less-than-16 group. However, the confidence intervals are so broad, that there's no basis, particularly are broad in the greater-than-30 population, that there's no basis for concluding that those patients respond better.

Obviously, because they start at a higher baseline, a PASI 75, the absolute amount of PASI change for a PASI 75 percent for a patient who is at 30 or 35 is obviously going to be much greater than for a patient who begins at a PASI of 10. But in terms of the percentage of patients who reach those criteria, no, we have no basis for concluding that there is any difference.

DR. TAN: So 30 may not be a good cutoff point. Is there an analysis done on the PASI itself? Instead of using 30 as a cutoff point, just looking at the PASI itself, whether the PASI is the same between responders and non-responders.

DR. WALTON: Oh, I'm not sure that we did the analysis that way, but given that within these subsets,

there really is not much difference, I would not expect that sort of inverse to reveal a difference because the PASI responders were spread out amongst all of the different baselines.

DR. TAN: I mean if you look at the PASI score itself as a continuous scale, do you see any interval? You know, a higher score may indicate a little bit higher response.

DR. WALTON: In terms of percentage or propensity to show a PASI 75 response, you're talking about? Sort of the dichotomized responder, yes/no?

DR. TAN: Continuous, not dichotomized.

DR. WALTON: Oh, in terms of the response, the points of response? Obviously, looking in terms of the absolute PASI response, points of response, that has to be greater with the higher your baseline because simply there's more room to respond and so that would show up. In terms of the fractional response, if you looked at the PASI 50 percent responders, we did not see any distinguishing by baseline with that either.

I know we're all looking for how we distinguish, but I'm afraid our analyses haven't been able to provide the insight into distinguishing, in terms of predicting, who's going to be a responder and who is not.

DR. TAN: Yes. Both sides of the question I

think is important. That has also been discussed. What are the characteristics of the responders, and also equally importantly because 80 percent of the patients probably were non-responders. So at what point of the time you can tell the patient it is time for you to switch therapy? So look at both sides.

DR. WALTON: I think that some of the Genentech data did speak to a little bit of that question in the sense of if one considers a complete 12-week treatment course, the information on continuing treatment beyond that in patients who have not responded well -- there were very limited amounts of additional patients who then became responders.

As to how early one could make that call, that analysis, I don't believe we've done, sort of a week-by-week analysis of present state as a predictor for 12-week state. We don't have that analysis.

DR. JOHNSON: Could I just illustrate the point that you've just made, Dr. Walton, with this data, which is, I think, the analysis you referred to, which is, in that extension study when we went to the second 12 weeks of treatment, we looked at response at the end of the first 12 weeks as a potential predictor of response in the second 12 weeks. I think the point that you made is borne out, that if you don't have more than a 25 percent response by the

end of 12 weeks, the likelihood that you will subsequently respond is extremely low.

So, in a way, to come back to Dr. Morison's question, one of the predictors of which patients to treat is the people who don't respond to drugs should probably not go into a continued treatment cycle, and at the same time, those patients should be watched carefully when you transition them to other therapies because they are at potentially greater risk, it seems, of the rebound events that we described earlier.

While I'm up, I can actually also show Dr. Katz's question now, if that's appropriate. Again, looking at that same study, we've looked at the 90 percent responders. So this is our long-term 3-year study, actually the 1 patient referred to. In this, we're looking at the 90 percent responders. So this is an open-label study. That's the caveat to this study. You see a slightly higher response rate in that open-label study. But proportionately I think it's instructive that of that 41 percent, about a third of the patients had a PASI 90, and as we followed those patients out, again using an intent-to-treat analysis, you see a larger proportion, about nearly 50 percent of the people who have that, maintain 75 percent response attaining a 90 percent response. This would be consistent with the data, at least

proportionately, for the major pivotal studies.

DR. STERN: Yes?

DR. PAPADOPOULOS: I have just a clarification to Dr. Morison. For the first two studies, randomized trials, the entry criteria specified that patients had to be clinically stable for 3 months prior, and in 2390 and in 2600, the later two trials, the entry criteria did not have that specification, but at least in 2390, as I saw, it specifically said under exclusion criteria, that they could not be in a state of flare, say. So for what it's worth, I just wanted to clarify.

DR. WALTON: I was just making the point that from those two observations, it tells us something about who we should be treating, at least at this point in time. So someone who's turned around and done the studies, of taking a bunch of patients who are in an active inflammatory flaring stage of psoriasis and treat them with the agent. At this point in time, I don't think we have the information to say if Mrs. Jones walks in and she's got roaring psoriasis which has been exacerbating over the past 4 or 5 weeks, it doesn't sound to me that this is the first agent I would think about.

DR. WALTON: We would agree that the studies of that have not been done with this agent.

DR. MORISON: I wasn't saying that the agent

may not work in that situation and I would suspect it won't, but I'm saying that shouldn't be an indication.

DR. WALTON: Right. It's not been studied. We don't know. We agree.

DR. STERN: One of the things that has happened which I hope we would correct a little bit is we've tended to concentrate an awful lot on the PASI as the endpoint. Remember that not everyone agrees and previous FDA hearings have stated that there are a lot of flaws, some of which have come forward today, that decreasing the PASI does not necessarily correspond with what in fact is happening to the patient in terms of improving their disease and improving their condition. So yes, it's important that we not try to put too much precision in an imprecise measure and look too much for this is changed.

There are a variety of characteristics of the behavior of the scale that in fact depending on what goes into a PASI of 30, in terms of extent versus thickness versus scaling, it's easier to reduce some PASI 30s than other PASI 30s. So let's not think of it as the gold standard. It is at best the brass standard and some people would say even less than that. I think it's one of the metrics we have, but I'm afraid we've gotten so much into reading more into it than perhaps is justified.

And with that note, Dr. Schmidt.

DR. SCHMIDT: In Houston, when we use the chimeric biologicals, when people develop antibodies to them, it decreases their ability to treat the condition, and so a lot of times, we give methotrexate in addition to the medications starting out.

These humanized biologicals also develop antibodies, but on these long-term studies, have the antibodies decreased the effectiveness or is this known?

DR. JOHNSON: There are two things about why you would be concerned about antibodies in these biologics, and the point that you're addressing is if that if you develop antibodies against the drug, then does that decrease the efficacy of the drug. So the first thing to ask is, what is the antibody that you're generating? Is it targeted against the actual complementarity-determining region of the drug? The assay that we have, with the 6.3 percent number that Dr. Papadopoulos showed, is absolutely aimed at that CDR region.

The next question is, how much of it is there? So the mere fact of being positive or negative is really a function of the sensitivity of the assay, and we frankly pride ourselves on our ability to make very, very sensitive assays. So if you look at the amount of antibody that would be predicted to actually have a neutralizing effect, the number of patients who have greater than 1,000

micrograms per ml of the antibody is in fact .8 percent. So it's very much lower than that overall number of 6.3 percent. In fact, in terms of the noise of the assay, there are a few placebo patients who actually recorded a positive assay. So it's an extremely sensitive one which descends into the noise range of the assay.

DR. SIEGEL: Yes. I'd just like to also make a comment about antibody formation and the clinical ramifications. I think it's important not to generalize from one biologic to another because the situation with one can be quite different from the other. I think you may have been referring to infliximab, or Remicade, where concomitant immunosuppressive agents do reduce the incidence of antibody formation, and antibodies there are associated with decreased efficacy and more adverse events.

We have experience with other humanized monoclonal antibodies where there have been antibodies formed and they have been associated with lack of efficacy. With other ones, there's less antibody formation.

So I think you can have some generalizations about how likely it is, but you have to look with each individual one, and with this particular product, we did not find that the patients who had antibody measured did not have efficacy.

DR. STERN: Are there are any other questions

by the panel to the sponsor or the FDA?

(No response.)

DR. STERN: Okay. I would like us to take no more than a 7-minute break and be back here at 10 to 3:00.

(Recess.)

DR. STERN: Ladies and gentlemen, we really need to start. We have 13 yes/no votes to take and a large number of questions for comment. So even if we stayed till 9 o'clock tonight, which we're not planning, it doesn't leave a lot of time for each question.

Ms. Topper, the executive secretary, has asked me to go through the questions for yes/no votes and then the comments about them. I think we can take a vote on the questions as they are, then have discussion, and if someone suggests perhaps that there's a better way of phrasing what the question is that more committee members might agree with, someone can suggest that after the vote. Otherwise, we'll never get through things.

Before we start, I realize that I cut off Dr. Ringel before the bathroom break and I think she had a last question.

DR. RINGEL: This is sort of a question and sort of a statement, and I'm not certain how appropriate it is for a setting like this, but I'm going to say it anyway, and that's to broach the question of medical economics.

All of these biologic agents are very expensive. I don't know how expensive Raptiva will be, but let's estimate perhaps $15,000 a year to keep someone on it. That's a low-end estimate for two reasons. First of all, there may be lab work or other doctor visits involved obviously, so that needs to be taken into account, but the other thing that's very important is the treatment effect, that this is not a medication that's 100 percent effective. This is a medication that's -- let's say the treatment effect is 20 percent. So that means 1 out of 5 patients will reach the PASI 75 or be successful on it. That means we have to treat 5 patients for 1 success. So we're talking about $75,000 or more to get 1 patient clear of psoriasis.

In this day and age where the monies available to treat serious medical conditions are very tight particularly, let's say, in my state because in Maine, these agents are being approved by Medicaid, for example, so to treat one Medicaid patient for the State of Maine is $75,000. I have to wonder how many children's immunizations could you buy for that, and I don't know that there's an answer to this, but I thought that it's very important simply to say it. So I've said it.

DR. STERN: Thank you very much, and I have some very good news and I misdirected you. The executive

secretary has corrected me and both she and I are breathing much more normally now, that there are really only three issues that require a yes/no vote and those are 6(a) and (b) and 7. Oh, 1 and 7. They are only 1 and 7.

DR. WEISS: A correction. Most of these questions are really discussion to get the consensus of the committee. The most critical question for voting is actually 7, where we try to highlight that we would like a vote on that question.

DR. STERN: I guess what we should try to do is try to elicit individual's succinct opinions about each of these questions. So if someone has opinions, whatever they may be about each of the questions.

The first question is: do these data, that is, those that we've heard today, provide sufficient evidence that Raptiva has efficacy in patients with moderate to severe chronic plaque psoriasis?

I think what I'd like to do is go around and you can always pass and we'll start in different places. So why don't we start to my right? Yes?

DR. WEISS: Can I also clarify for the committee and based on some discussions we've had, the question about risk and benefit is the question in number 7. We realize it's very difficult to really evaluate efficacy in the absence of safety and you put it all

together to make your recommendation, but to actually just separate things out, even though that's quite artificial, we really wanted the first question to engender a discussion just about the quality of the efficacy, the comparability across the four trials which came up in discussions with Dr. Tan and others and the effect size and those kinds of things. That's the nature of that first question.

DR. STERN: Dr. Schmidt?

DR. SCHMIDT: I feel like this does show efficacy, and I don't know what more to say about it.

(Laughter.)

DR. STERN: I think short comments are fine, or even none.

DR. EPPS: I think there's some supportive data. What I usually tell my patients is either it works for you or it doesn't.

DR. STERN: I'll pass.

DR. KATZ: I think we have to define when you say provide sufficient evidence, incontrovertible evidence, that it is better than placebo. So it has efficacy. I don't know that that can be questioned.

Always in the back of a clinician's mind is what was brought up by Dr. Ringel. Is it sufficient evidence of efficacy on a sufficient number of patients

that would be used? That is a very personal thing. 1 out of 5 patients get a PASI 75. You do that with many more things that are available.

Now, this is an additional in somebody who can't take methotrexate, who doesn't do well with light, who does terribly with topical therapy. I mean, for that occasional patient which is in practice rare, then it would be good for some people to have this drug. So I find it very difficult to answer this question of "sufficient evidence."

The other thing is that in practice just from a practitioner's point of view, people at medical centers are seeing a biased sample, and when you do a study like this, you're advertising for patients and to get patients for the study, you're selecting patients who have not been satisfied with anything else. Aside from the 80 percent that didn't get a PASI here, there's a bulk of people out there that do well enough with other treatment.

Now, granted, there's a need for more. We don't have good enough treatment for psoriasis for the more severe patients, as we have heard from the patients who presented today very eloquently. So I have great difficulty answering this, but I'd have to say that there is evidence. I don't know that there's sufficient evidence to warrant it.

DR. STERN: Dr. Sawada?

DR. SAWADA: Yes.

DR. STERN: Dr. Morison?

DR. MORISON: I'd say yes, and in light of the point I was making earlier, moderate to severe chronic stable plaque psoriasis.

DR. STERN: I think we'll get into some of our specifications later on in 6(a) and 6(b).

DR. BLAUVELT: Yes.

DR. DRAKE: Yes.

MS. KNUDSON: I am persuaded that there is a subgroup of patients that will be responders and I think yes.

DR. TAN: I will say yes. There's not a lack of statistical significance there and the size is 20 percent.

DR. RINGEL: I'd say that there's no question that this is statistically significant data. Whether it's clinically significant data, I would find it very difficult to say to the people who spoke here today and came from many miles away that they could not have this medication.

On the other hand, I have to hope that the clinicians who prescribe it will look at the data carefully and say there is 1 out of 5 chance that I will be able to produce a patient as happy as these are. So I guess in the

end, my answer is also yes.

DR. STERN: Why don't we then go on to question 2(a)? Dr. Ringel, I hate to pick on you, but we'll start in reverse order this time and for 2(a), the sponsor has proposed weekly injections without any specific duration of treatment.

In fact, if I may ask for a clarification, I believe you were asking for an indication for continuous therapy without at this time any limitation on duration. Did I understand in your opening statements that's what you were asking for?

DR. JOHNSON: Yes.

DR. STERN: Which is a little bit different than this. Please discuss the strength of the efficacy data on intermittent versus continuous use, and if approved, do the data support a recommendation for continuous administration? So I guess that's the question.

DR. STERN: Dr. Tan?

DR. TAN: Yes. I think as we have discussed, this is for those patients who seem to be responding to a therapy within the first 12 weeks, and it seems there's evidence they would continue to benefit. For those patients who are not showing any sign of responding, I think that what is presented, they would have little chance, a 10 percent chance probably, to be able to benefit

from this if continued. So there is limitation there. It cannot be used continuously forever.

MS. KNUDSON: I echo what Dr. Tan said, but I also want to say that I have a lot of concern about long-term safety data for this product. I would want to see certainly phase IV studies done and I would like a lot of evidence about long-term use.

DR. DRAKE: I think that question could use a little fine-tuning if it's approved with some good phase IV data. I'm not certain I know the answer. I think right now, there's a comfort zone at least from my perspective with intermittent use, and I notice your question 3, some of these are kind of the same, but question 3 is I think the problem is you don't want to just stop it abruptly.

So my sense is that it's probably best used as an intermittent dosage with a notion that you don't abruptly stop it. I think the outstanding question of can they use it for 5 years without interruption, I mean, I think it's like any other drug that goes to market. You're going to have to have some long-term data on it.

I would also just like to take a moment to comment on how many people could use it. I don't think that's material. I think we've seen 5 patients today that this drug would help. I don't think it's our job to decide how many patients have to benefit from it whether we

recommend approval or not. I do think it is our job to consider whether it is effective in any group of patients. So my sense is that it's certainly fine for intermittent. It needs maybe a little tweaking to know about how long continuous is continuous.

DR. BLAUVELT: Similar to Lynn, I think that there's no data for long-term continuous administration, but that shouldn't interfere, I don't think, with approval today because I think those are more appropriately done in phase IV studies. So I agree with her on that. I think what I've heard today is, in my opinion, it will not work intermittently. So I think we've seen enough that I would not be interested in intermittent use therapy.

Then I also wanted to comment, I guess, on efficacy. In these comment periods, people have been throwing 20 percent, 20 percent, but I'm of the mind that a PASI 50 is a clinically meaningful response. So I'm looking at this drug as helping a much larger percentage of patients than just 20 percent.

DR. MORISON: I would think the evidence indicates that it's efficacious for continuous use, but continuous use, we have no evidence that we can do it longer than a year. So I would say yes but not longer than a year.

DR. SAWADA: Again, I agree with my colleagues

who spoke earlier. I have a concern about continuous use therapy, although I don't think it should be intermittently used, given the presentations today. I think it's very important that if this drug comes to market, that the labeling of it is specific enough to tell the clinician, the every-day dermatologist, when they should stop when this medication does not appear to be working in that patient population and again the cautions about stopping this drug abruptly.

The other thing is, voicing Dr. Stern's concern at the very outset of this meeting, I think phase IV trials would be very, very important. Gathering the data in people who are on this medication is going to be very critical and the responsibility of the company to gather this data and what data they want to get from the practicing clinician. That has to be outlined as well.

DR. STERN: Dr. Katz?

DR. KATZ: Once again, the question really relates to efficacy data. So the strength of it? If 1 out of 5 PASI 75 is considered sufficiently strong, then yes. I think that's the criteria. Not PASI 50 because once you get to PASI 50, I think the market would take care of that anyway because PASI 50, lots of people get better with very noninvasive treatment, 50 percent better. So that's not the role for a drug like this. So I think we should use

what is used as the gold standard of PASI 75, and once again, yes, if it's efficacious and it seems like it would have to be used for continuous use.

Safety will be another measure. Don't forget, we only have 2-year data on 200 patients. So we must not lose historical perspective of all of the drugs that have come out and done harm, been removed from the market, and here we have only long-term treatment with 200 patients.

But my answer to this is yes, it's efficacious.

DR. STERN: I would agree that this is not a drug to go on and off. This is a drug to use until you decide to use something else and taper the person off. I think there's abundant evidence for that and the rest of the points, which I think we'll get into on the safety side, and the limitations of the data about how long in fact it'll keep on working, given what we're presented, we'll discuss as we go on.

DR. EPPS: I think there's support for -- I don't know about intermittent -- maybe for the more shorter courses. I don't know that there's enough data supporting long-term continuous therapy at this time.

DR. SCHMIDT: The longest study that they had was 3 years. I'd like to see us extend this thing to 3 years and then look back and say can we have it go longer, if we could do something like that.

And then I'd like to comment on this labeling thing about the cost-benefit, that clinicians like myself, when you look at a medication, you want to look and see how many people are going to clear versus how much it's going to cost. So I think we need to include something like that in the labeling, but I'd like to see it go for 3 years at least first and then have studies later to continue it.

DR. STERN: Dr. Ringel?

DR. RINGEL: In my mind, there are two points on the opposite ends of the spectrum that are pushing me in either way. One is this issue of unknown side effects. I think that at 6 months, they had accrued some 900-some patients. I know that's not a lot from a safety standpoint, but I do think that that does give you some idea that for at least 6 months, that these patients really didn't seem to be getting into too much trouble.

On the other hand, for continuous therapy, there's an argument for it. First of all, the patients seem to want to use it longer than that. They're doing fine. They're not getting any side effects, and as a clinician, it's very hard to look someone in the eye who's doing just fine, happier than they've ever been in their life and say, sorry, you need to get off of it. I think that's been a problem with all of our psoriasis therapies.

The other issue is this business about the

flare. I don't know if I believe this is real. I really don't. I think that if you take the definition of rebound as the company has, saying this is more than 25 percent worsening over their baseline PASI score, the percentages who had a rebound for the placebo were the same as they were for the drug. So I'm really not sure that this is really rebound. I think that they're just getting worse and it takes, what is it, 8 weeks to start to get better again, so then people started to drop out. So it looked like they didn't do so well with that second course.

I'm not really sure that's something specific with Raptiva. I suspect that that would have happened with a lot of drugs where it takes awhile for things to work. People with UVB get disgusted. They've been doing it for 4 weeks. They're not that much better, so they drop out. I'm not sure that this drug is really giving a rebound. So I guess I'm not as worried about stopping it as some of the rest of you are, and I guess those two things are weighing on my mind.

So what I'm coming down to is kind of a compromise. It's not a good compromise, but a compromise, saying that people would like to use it, we don't know the side effects. We have 1,000 people at 6 months. Oh, let it go for 6 months, then we'll collect more data, see how it goes.

DR. STERN: Thank you. Since the FDA did not adhere to strict numbering and gave me two number 6's, I'm going to make the first number 6 number 3 and we're going to go on to the safety of long-term continuous therapy because at least the way I think, you want to think globally and then get more specific about safety issues.

DR. KATZ: (Off microphone.)

DR. STERN: Oh, I think since most people said continuous therapy was the way to go, that it was sort of moot.

So 6, safety of long-term continuous therapy, and shall I read the introductory paragraphs? Does everyone have a copy of the questions? Well, let me read the introductory paragraphs.

The current paradigms for the treatment of psoriasis requiring systemic treatment include continuous long-term treatment and intermittent or rotational therapy. The latter minimizes exposure to individual agents and may ameliorate drug toxicities that are potentially of a cumulative nature, i.e., hepatotoxicity with methotrexate, nephrotoxicity with cyclosporine, skin cancer with PUVA.

In the efalizumab safety database, approximately 2,400 patients received efalizumab for 12 weeks, 939 for 24 continuous weeks, and 218 for 1 year of continuous therapy. These number are higher than the

minimum ICH recommendations for safety database for products intended to be used chronically. However, the agency may request that larger numbers of patients be exposed, if warranted, based on specific issues that require further evaluation.

That's the FDA's prologue.

Here is the first thing for discussion. Please discuss whether the submitted safety information on efalizumab use is sufficient to assess safety questions relating to long-term continuous treatment with efalizumab.

I think what we've heard just a moment ago is everybody thinks of long-term as different intervals. At 2:30, I thought long-term was waiting until we could have a break, and so let's be specific and let people, when they talk about long-term, define what they mean about it in terms of continuous use. So if long-term means 6 months to you or a year to you, or yes, I'm comfortable with long-term if you mean up to a year and I'm not comfortable with this, please specify that in addition. Otherwise, we'll all be using different concepts of what we mean by long-term.

DR. SCHMIDT: Long-term to me means 3 years, and yes, I think that the safety data is sufficient with the problem with the platelets and some of these other things to assess the safety questions, and then one thing

on specific issues that worried me a little bit was that one guy who developed the transverse myelitis and there were a couple of these kind of funky neuritises and things. I was a little bit concerned about that, that we need to kind of keep an eye on that.

Then as far as the comment on potential need for long-term monitoring, I think that any of these things would require long-term monitoring, especially the platelets, and so I would have some kind of recommendation -- and I guess you work with the manufacturer -- but at least a chem panel and CBC say every 6 months when somebody's on something like this and a physical examination.

Thank you.

DR. WALTON: Dr. Stern, may I add a clarification to the question, to the last portion of that question? As part of the discussion for that, some of our thinking was also questions about whether or not assessment of immune responsiveness needs to be looked at, not simply safety monitoring for an adverse effect but the ability for immune responsiveness in the face of continued product.

DR. STERN: Dr. Epps?

DR. EPPS: As for the safety data, I'm not sure to my satisfaction I've had enough. There were some complications, as I discussed earlier, some safety

questions I still have. I would probably want more. As far as long-term, in pediatrics 50 or 60 years is what we consider long-term. Obviously, we don't have that long to wait. But that's a separate question as well.

I would consider monitoring or following all the things that are specified not only, I guess, in 3, 4, and 5, and certainly there are some potential risks not only with infection, malignancies, and thrombocytopenia. Fortunately, no one had a stroke or anything, but there are some risks there.

Also, long-term monitoring immune function, I guess that kind of remains to be seen. We just don't have enough forward data.

DR. STERN: This time I will take my turn. I think that the information we have on the safety of this drug in long-term use -- by that I mean for more than a year -- and if this drug were only safe for a year, I would say although efficacious, it would represent not very much of an addition to our therapeutic armamentarium. So in terms of long-term use, one has to look at a variety of issues.

First of all, there is the latency between first use and the ultimate occurrence of the event and that's particularly important for non-melanoma skin cancer, particularly squamous cell carcinoma, and in fact, although

there are two types of lymphoma that are associated with immunosuppression, one, the EBV-related which often comes out early in high-dose patients, I think there's less data that tells us whether a little bit of immunosuppression delays that, and another with chronic immunosuppression, not the EBV-related, of which I believe there was one case that we saw in a treated population here.

So we have skin cancer in a population that has substantial prior exposure. It's going to take some time for that to emerge. We have lymphoma, and then we have infection, and we have all things that are going to take years of studies. If you do the power calculations, based on the incidence of, for example, lymphoma in the general population, you're really having to talk about a complete follow-up on probably between 5,000 and 10,000 person-years of follow-up to detect a 2-to-3-fold increase in risk and you'd certainly want to detect an increase in risk as little as that. So I think without long-term safety studies, this drug is a drug that's an unknown quantity.

I'll make one further editorial comment or advice comment. Over the last year or two, there's been a lot of debate within the agency, between the agency and the government, and in the press about post-marketing surveillance and its efficacy and in fact post-marketing commitments and the degree to which they are completed

either technically or in a way that in fact leads to interpretable information. We know that the agency does not have the power to withdraw a drug based on a phase IV commitment not being fulfilled in the way it would like it to be.

So I would suggest that part of labeling in fact should be to give the clinicians and the public the information that we have and don't have that specifically says, in the case of this product from my perspective, there are concerns about an increased risk of infection which may be severe, of lymphoma and skin cancer which we do not know about and that that should be a warning and that there are ongoing phase IV studies to evaluate this and that part of the labeling should only be withdrawn when the studies are completed that in fact allow you to quantitate each of those risks.

So I think you can't take drugs away, but you can label drugs to say what you know and don't know, to me about the three most important and potential long-term effects of this drug, if it's used long-term.

DR. KATZ: Considering that only 218 patients have been treated for 1 year and the potential of problems, I would like to see it studied for a longer period of time. What long-term would be, I don't know. I don't have experience with that, but 2 or 3 years, with a greater

number of patients than 218 patients.

DR. SAWADA: I have a question for the FDA. Perhaps they can tell me. How would you propose monitoring for the immune response?

DR. SIEGEL: With other potentially immunosuppressive products in the past, we've asked companies to do randomized controlled trials post-marketing looking at the ability of patients to mount an immune response to vaccines, either experimental vaccines or therapeutic vaccines, depending on the level of concern that the responses would be diminished, and we've gotten useful data about T and B cell function of patients on these potentially immunosuppressive agents. We're interested in the views of the committee about whether this would be important information to collect and whether you'd find it valuable.

DR. SAWADA: Given that information, I think that is important information to gather. Again, trying to ascertain what long-term therapy is, again it would be very hard to say no to a patient who's doing very well on a medication and say, sorry you can't have it, you met your 3-year deadline. But I do think we should take this opportunity to gather the information from the people who are on this therapy, and God forbid, I don't need another register, but perhaps something of that nature might be

warranted in following this particular medication.

DR. MORISON: I guess my definition of long-term at this point in time is a year because that's all the data we have. Longer long-term, I'm thinking in terms of 5 years of a phase IV study following a significant number of patients up as you were mentioning.

With regard to issue (b), I think that, picking up on Andrew's point, we haven't really used animal studies here very effectively. For instance, the question of photocarcinogenesis can be easily investigated in an animal model. A simple study, cheaper than doing it in humans, is going to give you a lot more information in terms of risk of exposure to UV radiation, which I would point out all psoriatics are exposed to UV radiation in excess because they either use ocean beach during the summer UVB or PUVA therapy and all of those are photocarcinogenic. So I think you can get a lot more information from animal studies than you have so far, including exposure to infections, and see what exactly happens in the mouse model you're using.

With regard to the third thing, I think that's fine. Immunizations. If you've got a contact sensitizer other than DNCB, you can see what the ongoing response to antigens is. I don't think there's much advantage in doing recall antigens because that seems to raise more questions than they answer.

DR. BLAUVELT: I agree, 1 year. I think the labeling should say that beyond 1 year, there's limited safety data.

I'm surprised. I was just going to say that I would like to see skin testing done with recall antigens maybe every year in post-studies just to give some information or with a neo-antigen also looking for its effect on a primary immune response.

DR. DRAKE: Well, I think I maybe didn't make myself clear earlier. When I think of intermittent, it doesn't mean stop and start, just stop cold turkey. I think you've got to have continuous therapy of some sort. Can you use this drug safely for a year? It would seem so. But as I mentioned earlier, 5 years, I don't have the answer for that. I think data needs to continue to be collected. Maybe rotational studies. It's clear you can't give them this drug for a year and just stop and we've heard that from everybody.

So I think any additional information that can be collected would be useful and frankly there's a lot of information that needs to be collected before we know exactly where we are on this.

MS. KNUDSON: I would think that anything longer than 12 months is long-term, and I do continue to have safety concerns about the drug. I'm not entirely sure

how one would continue to monitor it, but I would think patients should be monitored carefully.

DR. TAN: There's a little confusion. There are two long-terms. A long-term use is the duration of the therapy, and then there's a long-term follow-up after that. That's the two things we're talking about. I think the NDA has provided data on the 1-year use of it. So that's the safety data our decision can be based on. But in terms of how long it should be used, we don't have data on the 3-year use and the long-term follow-up after that. So it could be 5 years and those data should be collected.

Also, it's important to collect the data on immune response monitoring and that may shed light on the categorization of the patients, responders and non-responders, and may help us in the future.

DR. RINGEL: When we're talking about data at 1 year as being long-term, well, we have 200 patients in that category and that means we will be able to pick up a side effect of .5 percent but no less than that and these side effects that are serious that we're talking about, certainly many of them are going to occur at an incidence of less than .5 percent. So there's no question that we really don't even have good enough data, safety data for a year. I'm stretching 6 months. I guess that's why I said that, but I was really even unhappy with a year.

In terms of long-term follow-up, I think there are two categories of long-term follow-up. There's long-term follow-up for the phase IV studies, and there's long-term follow-up for the patients who are not in phase IV studies. For phase IV studies, I would think at the very least the question of vaccines and whether or not you can immunize people when they're on this medication is an issue. The platelets, getting anti-platelet antibodies, following up with anti-Raptiva antibodies, following up with skin exams for squamous cell carcinoma.

The other thing I'd add is some follow-up of a rheumatologic profile for autoimmune diseases. We are increasing the CRP in all of these nonspecific inflammatory markers and you wonder is that going to mean something for somebody who has lupus. What are we really doing to these patients? So I would add that.

In terms of people who are not going to be in the phase IV studies, at the very least, I would recommend getting intermittent platelets and a skin exam.

DR. STERN: Any other comments?

DR. BLAUVELT: I was a little bothered when the company did not recommend any laboratory monitoring in the patients, like we're going to give this to them and see you later. I think with this drug at least a CBC chem profile every 6 months is not much at all. I don't know because we

just don't know long-term and so I think we need to gather that data, so we do need to recommend that some of these laboratories are taken I think at more regular intervals to collect the data, to know what happens in the long term.

DR. STERN: I do think to my mind, although it's been explained, it strikes me that if I had a patient who in their first 12 or 24 weeks of therapy either had a trend towards a decrease in their platelets or more than a doubling of their lymphocyte count, I would worry that they're not behaving like most patients are, and although I wouldn't know the ultimate clinical significance, if someone's lymphocyte count increased 4-fold, I would say that's really peculiar or if they went from 300,000 to 150,000 platelets, I'd say that's worrisome, too. I guess I'd rather find out about it in the time that some of these events occur, which are 6-8 weeks into therapy, than 6-8 months into therapy, particularly since with a relatively small number of actual person-years of exposure, we have seen the 8 or 9 cases of only at best partially-explained thrombocytopenia, and we don't really know what that's going to be long-term, but we'd like to detect them short-term.

DR. DRAKE: Rob, I want to echo what you say. I think 6 months is too long to monitor these people because there's a lot of unexplained lab. There's

increased alkaline phos. There's some liver function studies that are little abnormal and the thrombocytopenia. It's going to occur pretty early, and I think knowing about that early is far better than knowing about it later. It doesn't mean you don't want to use the drug in a group of patients, but if somebody is having trouble with it, above all else do no harm. I think that's part of our philosophy.

I would like to see this made available to people who have this disease, no question. It's a terrible disease, we've heard from our patients. But at the same time, we want to make sure that that individual patient is not reacting in an abnormal manner and it's going to cause them harm instead of help them.

So I would recommend monitoring at least for a period of time, until we know more about it. It would really make perfect sense to me to check them early on.

DR. STERN: Have we at least addressed your issues or the issues about either long-term safety or about specific immunologic monitoring in the detail you'd like or would you like to have more?

DR. WALTON: Yes, I believe we've heard the discussion in this general sense. Although some of the comments have touched on some of the specific item questions, I think I would like you to go back to the

individual item questions.

DR. STERN: The next thing I was planning to do is go back to the old number 3 and move forward. I just thought sometimes it's useful to get a global view of long-term safety and then get into the specifics. So our plan is to go back to number 3 --

DR. WALTON: Thank you.

DR. STERN: -- which is the psoriasis-related adverse events. Here again, since not everyone has the questions, I'll read the preamble.

Among over 2,700 psoriasis patients treated with infliximab, including those during the placebo-controlled and extension studies, 19, 0.7 percent, experienced a severe adverse event of psoriasis. Some of these occurred during treatment with infliximab but most, 14 of 19, followed discontinuation of the therapy.

DR. WALTON: I'm sorry, Dr. Stern. I think you've been too familiar with too many of our products. You keep saying infliximab.

DR. STERN: Efalizumab. I also have a little bit of a speech impediment.

DR. WALTON: If you would like to use Raptiva?

DR. STERN: Could I call it Raptiva?

DR. WALTON: That would be perfectly fine.

DR. STERN: Someone told me I shouldn't use it.

Okay. Thank you.

DR. WALTON: There are 1,600 different USAN names and they all look the same.

(Laughter.)

DR. STERN: Did you say Celexa or Celebrex? Is it my mood or my joints?

Psoriasis-related adverse event of any severity, serious and non-serious, occurred in 3.2 percent of Raptiva-treated patients and 1.4 percent of placebo patients.

There are three questions relating to this information.

Do these data suggest a signal with respect to rebound disease worsening in a proportion of patients subsequent to withdrawal of Raptiva?

If licensed, how should this information be conveyed to the physician in the product labeling?

The third is, should the sponsor be asked to develop more comprehensive data regarding psoriasis rebound? If so, what specific studies or data collection would be potentially useful in -- can I change this to quantifying and managing this risk?

DR. WALTON: Yes.

DR. WEISS: Yes.

DR. STERN: Why don't we start with Dr. Katz?

We'll go that way and then we'll go that way?

DR. KATZ: In answer to (a), the answer is yes.

Answer (b), it should just be conveyed in the labeling if the drug is approved. I mean, it's the risk of the use of the drug and the risks.

In answer to (c), I think we've been shown enough data on intermittent use to tell us about that, that you can't use it for 12 or 24 weeks and stop the drug. So I don't know that they have to develop more comprehensive data on this finite being different from the other long-term risks, like who else is going to develop thrombocytopenia or lymphoma and so forth. Here, I think it's finite. We have it in front of us. So I don't think they have to spend more time on that, and that would be my answer.

DR. STERN: May I ask the sponsor an informational question? What proportion of the total treatment groups were U.S. versus Europe and what percentage of the hospitalizations were U.S. versus Europe? I should say non-U.S.

DR. JOHNSON: All of the studies were performed in North America. It was a very small proportion in Canada.

DR. STERN: The reason I asked that question is the criteria for psoriasis hospitalization varies

substantially between the United States and Europe, and my interpretation of this number of hospitalizations in the United States in fact is that it's a very strong signal of people having very substantial and clinically significant flares, whereas in some other countries, it doesn't take much to get into the hospital when your psoriasis worsens.

So to me, this is an extremely strong signal of not just some people getting a little bit worse but at least this subpopulation having the kind of flare of disease that keeps both the patient and the doctor who has been administering or withdrawn the drug up at night.

DR. DRAKE: May I ask a point of clarification? When it says, how should this information be conveyed in the labeling, what are my choices? Are we suggesting a black box or a warning? I don't understand quite what they're asking me.

DR. STERN: I think they're asking for your best advice. So it's an open-ended question and whatever your best advice is.

DR. WALTON: I think from a sense of how concerned you are about this information, how much you believe this information is clear in its interpretation can inform us on how prominently and how strongly this needs to be discussed.

DR. SAWADA: As a practicing clinician, I

certainly would like to see this very much emphasized. If it takes a black box, it takes a black box. I think it's something that we shouldn't ignore and certainly would bring to my attention not to suddenly stop this medication and not to follow my patient closely, especially since we don't have a lot of data regarding this effect, but it's suggestive that it's a serious effect. I would like to really emphasize to the busy practicing dermatologist that this is something that they shouldn't ignore.

DR. MORISON: I'd go along with what Rob said, because I can't remember back to the last time I put an erythrodermic or a generalized pustular psoriasis in hospital just because of the hassle of getting them in the hospital and keeping them in the hospital. So these patients clearly were hot. So I think that the clinician has to be adequately warned.

I've got no doubt that these were significant rebounds of the type you see after a person is pulled of prednisone or a person is pulled cold turkey off of methotrexate. So I agree entirely this should be very prominently featured in the labeling.

I don't think we need any more information to tell us this was a rebound because although it was sort of hidden into the proportion of patients who are on placebo and the proportion of patients on active medicine who got

25 percent worse wasn't very different. We weren't told how much more than 25 percent worse, but when you saw the breakdown on number of erythrodermic patients, the number of generalized pustular patients, they were all over on medicine. They're all over on active principle. They weren't on placebo. So my guess is that those two numbers of 18 percent or whatever it was were sort of irrelevancies because it's not explained exactly what went on.

As far as (c) is concerned, I think that you could gain information by having the sponsor direct some studies towards developing means of getting patients off the medicine. In other words, if you decide to stop the medicine, how do you go about it? They may have information already on that, but which drug would you switch them to, how long do you keep them on combined medications?

Studies along those lines are going to give you the most information because saying they should be on another psoriatic med doesn't tell you whether that should be a touch of Lidex or a strong course of PUVA or UVB. So studies directed along those lines are going to give you the most information. I don't think we need more information about what happens.

DR. BLAUVELT: Well, I'm going to respectfully disagree with what's been said on this issue so far in that

to me, we saw data that the majority of patients after treatment slowly get worse gradually over a 2-month period, and I think that's the majority of patients, at least that's the data I saw, and the individual cases of erythrodermic and pustular, which were indeed impressive, I see as more of an idiosyncratic phenomenon that not a general phenomenon that is specific to the drug.

So to me, the data don't speak to this being a general problem of this drug. I think it's more of an idiosyncratic thing that could be mentioned in the labeling but because it's not a general feature, to me I wouldn't emphasize it as much as the other speakers have said.

DR. PAPADOPOULOS: I just wanted to clarify part (c) and one of the topics I think would be useful for us to get information on would be what types of studies or data collection could help characterize what patients are most at risk for these flares. So that was part of I think what we're asking in part (c).

DR. STERN: Well, the problem with that is a power problem. You have something that in this open study has an incidence of about .7 percent among all those treated and who have been withdrawn from therapy. The at-risk group, you have no clear signals, as I understand it, when you went through case-by-case beyond what Ivor shared with us, and with such a low incidence event, unless you do

extremely large-scale studies, you're not going to be able to find out which are in fact the significant risk factors, particularly, as I think Ivor sort of pointed out, so many of these things are co-correlated in terms of characteristics, treatment patterns, et cetera, et cetera, that seem to go together.

So I guess if time and money were no object, it would be very interesting to do, but in my laundry list of priorities beyond warning people that -- I think you can have a fairly robust estimate of the incidence with sudden withdrawal of flares of psoriasis sufficient to have hospitalization of between .5 and 1 percent of people withdrawn. I bet the 95 confidence intervals are almost exactly that.

You talk about how serious those are, and sure, it would be nice to know. As has been suggested, ways to find out how to reduce this would be nice, and if you can have robust studies that show you've eliminated, terrific, but I don't think it's a good use of either the agency's time or the sponsor's time to try to come up with risk factors.

I would for one disagree with Andy about how often this occurs in clinical practice. I find that in my clinical practice, it's a rare event, treating a fairly large number of people with moderate and severe psoriasis,

to have flares that, at least by process variables, are as the majority of the 19 that you described in withdrawal to this agent. So I think it's a really rare event and this is unusual and has been characterized with a few other agents that we've now specifically, not through labeling but in other ways, warned practitioners how to avoid that event. We just have to warn about it.

DR. DRAKE: Part (a) suggests a signal about rebound. I think the answer is yes. Are all of them serious? No. I think it's a small amount that's serious, but I think the vast majority of these patients, at least from what I've understood, are going to get worse over the next 2 months. So yes, I think there's a rebound.

I think the problem with the ones that are serious is that they're quite serious, and I think the physicians need to be warned that in a small percentage that this can happen, so that they're paying attention and don't just sort of say it's another okay thing to use. So I think at some point, they need to be aware that it's tiny but real or potentially real.

Then when you ask about specific studies, I think further looking at tapering down the dosing, either by frequency or by actual dose, milligrams per kilogram. Can you move these patients into a maintenance phase and hold them? I don't know the answer to that. What are the

alternatives? Can you move them into almost any kind of maintenance or can you actually institute a rotational therapy where you move into even one of the more toxic systemic therapies but you're able to limit the amount of time they're on it? I don't have the answer to that.

So I think that rotational dosing, tapering and adjusting and just looking at how you can maintain them is important. So I think you have several options for design studies, but I guess the first thing I would approach is can you reduce the dose either by frequency or milligrams per kilogram once you get them clear. Could you inject them once a month and maintain them once they're clear? I don't know the answer to that.

DR. STERN: Well, I think the sponsor presented some small data on the use of essentially an average of a half milligram per kg, and I believe that Dr. Krueger, if we can wake him, was not very optimistic about the efficacy of that as well. Do I recall correctly?

DR. DRAKE: That's a good point, but it was my understanding that was in the clearing phase. I guess I'm asking what happens if you get them clear. Does that proposition still hold?

DR. KRUEGER: I think it would, and in fact, it might be mitigated in the exact opposite direction because blood vessels actually begin to shrink and you lose some of

your fenestration. So you're going to have a little bit harder time driving that gradient of antibodies into tissue. So I think the dose is about right for both induction and for maintenance.

DR. STERN: Thank you.

DR. DRAKE: So that wasn't such a good idea.

(Laughter.)

MS. KNUDSON: I do think that there is rebound, small though it may be, and I think that physicians should certainly be alerted to this fact in the labeling, and I'll pass on (c) because I cannot decide what kind of studies.

DR. TAN: I also think there is an indication for at least rebound. I really would like to have these statistics reported in the label. I think now a lot of patients are becoming very educated and sophisticated. They can appreciate the numbers.

In terms of (c), I think a more focused study, like a case cohort study, may be useful.

DR. RINGEL: In terms of this whole issue, I guess my problem is that I still don't know what the definition of rebound is. Is rebound simply going back to the original PASI? Is it 25 percent worse than your PASI? Just what is it? I did hear the data from the company that said 25 percent worse -- in other words, if you've had the 12-week course, you go off of it and then see how many of

those people are 25 percent worse than their original PASI, then you can't tell the difference between the treatment arm and the placebo arm. On the other hand, if you defined rebound as the PASI plus 50 percent or 75 percent worse than the PASI, you might see different results.

So I guess what I would do is take the 2058 which was the study and play those out. What percentage of the placebo and the treated group went back to their PASI? 1 percent went back to PASI minus 25. What percent went back to minus 50?

Eventually, I mean, what I think's going to happen is that the treatment group and the placebo group are going to be about the same, and then you're going to get this severe blip when you get to like 100 percent worse than the PASI you started out with and those are going to be the people with the erythroderma who went crazy. So I think there is going to be a difference, but I think you're just going to have to look at the data and play it out.

DR. EPPS: In respect to (a), it does suggest a rebound or disease-worsening. Yes, the physician should be alerted to it. I do think it's significant. The patients who did have a psoriasis adverse event, over half of them had erythroderma, pustular, or guttate which were specifically exclusion criteria. Those patients were not included in the study and yet that is what their flare

consisted of, and I think that's significant. As I said before, I think it was significant that quite a few of them were also hospitalized and it's pretty tough to get people into the hospital these days.

As far as additional data, although it wasn't presented, it may be in the company. I know we spent a lot of time talking about PASI and other scores, but where do we have a body surface area or distribution and who responded and who didn't respond and perhaps if they looked at those patients and told us what was going on, maybe it's there and maybe additional studies are needed. I don't know. We just haven't heard it.

DR. SCHMIDT: I think rebound is a real thing, and in clinical practice, the patients that I see, and psoriasis is really amazing for this, that whenever you stop someone with some of your stronger agents, you really risk having a flare. So at least clinically I always have somebody on a low dose of something else, and I never stop anything, even topical steroids, I taper them. So I think that this signal to rebound is a cause for concern.

I don't think that it should be in a black box, but I think it definitely needs to be mentioned somewhere, and also I think -- and this is the one thing that I have to admire about the pharmaceutical industry -- is when these things come out, there's a lot of information that

the drug reps bring to you and this should be something that should be brought out, that this isn't something that you just stop.

As far as these studies, to study the rebound and offer suggestions as far as how you treat some of these things to keep somebody out of the hospital, I think that's probably a good idea.

DR. STERN: May I just follow up on Dr. Epps' point which I think was an excellent one? One difference, at least in my clinical experience with particularly methotrexate since I don't use very much steroids, is the people who have bad flares are patients who had unstable disease before you treated them, and here we have a treated population that was basically by entry criteria stable plaque-like and have basically changed the kind of their psoriasis to a more unstable kind.

So I think there are two things. One is a general warning about the incidence of people who flare substantially afterwards. And the second is what I don't have data to prove but I would guess is higher-than-expected in the natural history of the disease of people changing their type of psoriasis from stable plaque, in coincidence with discontinuing the medicine, to a more inflammatory, more bothersome, and harder-to-manage kind of disease which I think is a second level of warning that I

think you stated very clearly and I think should be emphasized.

DR. BLAUVELT: Since I was one of the more dissenters, I wanted to clarify my opinion now that everybody has spoken. I think we think of systemic prednisone and cyclosporine as two classic drugs that, if we stopped abruptly, the majority of patients -- the majority of patients -- are going to have bad flares, whether you call it a rebound or not, bad flares. And for this drug, the point was that I don't think the data for this drug is similar to what we see with prednisone and cyclosporine.

What I see is that with this drug, to me, the data suggests that the majority of patients are like other drugs; the patients eventually gradually get worse when the drug is stopped. Not that these severe cases don't occur, I acknowledge that, it's just it's not like prednisone and cyclosporine. I think it's the rarity of it that I was trying to emphasize, that you can put the numbers in, that would be fine, but it's not a general phenomenon that patients are going to have bad flares when they stop this drug.

DR. RINGEL: As people were talking and frankly even as I was talking, something has occurred to me, that we're all recommending that this drug not be stopped

abruptly and that you need to start the patient on something else which is just great. But that means that there needs to be an overlap period, and we don't have a clue what medications are safe to use concomitantly with efalizumab and we have no idea how long that overlap needs to be. So as a clinician, you're going to tell me not to stop it abruptly, and I'm going to say yes, so what do I do, and I don't think we know.

DR. PLOTT: Just a point. In the development of these products, we do things that we don't normally do in clinical trials that you would never do in clinical practice, and one of those is exemplified here where the drug is stopped abruptly and patients are followed. Part of that is to find out, well, what happens, and what happens is reported here and being considered.

So one of the lessons, as Dr. Lebwohl pointed out, was that we learned that we shouldn't do that. So what you've seen is that other trials that were done subsequently were designed differently with other follow-ups and other dosage regimens. But I think it's important to look at the context that some of these events occurred.

DR. STERN: On to number 4, arthritis and other inflammatory adverse events. Among all patients treated with Raptiva, 15 cases of serious adverse events of arthritis representing 0.6 percent of the study population

were observed. These included one case in association with other findings of inflammation, fever, cellulitis, and a positive ANA. None of these cases occurred during the placebo-controlled portions of the clinical trials. All occurred during the extension studies, i.e., after 12 weeks.

The proportion of patients with arthritis-related events of any severity, including events of psoriatic arthritis, osteoarthritis, and unspecified arthritis, during the placebo-controlled portions of the clinical trial were comparable between the placebo-treated patients, 2.2 percent, and the patients treated with 1 milligram per kg of Raptiva, 2.4 percent. However, there was a suggestion of a higher proportion of patients with arthritis-related events, 3.9 percent, among those who received the 2.0 milligram per week dosage of Raptiva.

Rare cases of other inflammatory events have also been noted in association with the reuse of Raptiva, including transverse myelitis, one case; interstitial pneumonitis, one case; and idiopathic hepatitis, one case.

The two questions here are our opinions as to whether do these data raise concerns regarding the risk of arthritis and other inflammatory adverse events. And secondly, if they do raise such concerns, please discuss whether specific efforts on the part of the company are

warranted to obtain additional information on risk management and consequences of inflammatory adverse events. If so, what types of additional studies and/or databases would be most useful?

Could I ask if anyone from the FDA could give us a one-minute list of associations between increased C-reactive protein and adverse health events? I remember that high C-reactive protein makes it more likely that a person is going to have a myocardial infarction. That is, there is an association between those as a predictor of that. It's obviously associated with all types of inflammatory illnesses as a non-specific indicator of ongoing inflammation, but can one tell me in terms of predictive studies when one looks at a population and takes out people with higher levels of C-reactive protein, what are the adverse events that they're more likely to encounter?

DR. SIEGEL: I'm not sure if we're going to be able to give you more information than what you've already mentioned. There have been some studies suggesting that patients with higher CRP levels are at more risk of cardiovascular events, and it's unknown exactly what the interpretation of that is but that has been observed as a risk factor.

This is a somewhat different situation, of

course, because that's naturally-occurring elevated CRP. This is one induced by or associated with a therapeutic agent and whether the implications are the same or completely unknown. We don't have any additional information than that. Of course, higher CRPs are associated with inflammatory conditions, but that again may be quite different than the situation here.

DR. STERN: But I think the conservative assumption, just as when we give drugs like retinoids that increase triglycerides and cholesterol, we're worried that by increasing those levels, we are in fact recapitulating the cardiovascular risk factors than if you get it the old-fashioned way by the wrong diet. So I think that's the conservative assumption, that if there are population associations and if you raise it through some other than the endogenous mechanism, you might be at least as concerned that those associations might pertain in the population.

DR. SIEGEL: I think the situation here may be a little bit different. Some of the situations that you're talking about would be cases where raising some lab value or some condition is associated in a pathogenic way with a bad outcome. Like if something increases blood pressure, blood pressure itself is thought to be associated with bad outcomes.

CRP, I think, may be a reflection of inflammatory condition and may not in itself cause bad outcomes. So we don't know whether the elevated CRP would be the same as what you're talking about, elevated triglycerides, or an elevated blood pressure would be.

DR. STERN: I'm trying to come up with a variant on the order without getting confused. So why don't we start with Jimmy?

DR. SCHMIDT: I think that if we stick to the 1 milligram per kilogram, there wasn't that much difference with the arthritis and the placebo, and I understand that probably the 2 milligram per kilogram of body weight dose really doesn't add anything. I was really disappointed that this stuff really actually didn't help arthritis, but I guess if it doesn't affect the monocytes or the macrophages, it's not going to. So yes, I'm a little bit concerned, but I think at the 1 milligram per kilogram of body weight, I don't think that this is going to be a big concern.

And then whether specific efforts on the part of the company on the risk of inflammatory adverse events, yes, that's something that did concern me as I mentioned before, and I think there should be some effort to monitor these things.

DR. EPPS: At the 1 milligram per kilogram

dose, it's not that different from placebo, 2.4 versus 2.2 percent. So from what I understand, we're only considering the 2 milligram per kilo per dose per week. So I can't say I'm very concerned. I mean there are a lot of other medications, including antibiotics, and things that cause arthritic-type symptoms at times. I don't know whether or not it was characterized enough to know whether it's a psoriatic arthritis or some other kind of arthritis, but I guess that would go into (b) which means just monitoring, I guess phase IV.

DR. WEISS: The reason why we put in the information of 2 milligram per kilogram dose is not because there's been a thought on the table about whether or not that dose should be recommended, but sometimes when you see a dose response, it just puts it into more whether or not this has got more biological plausibility. We realize the 1 milligram is very similar, but again the information in the database is relatively small, and so we're looking at information that might give you some idea about a signal.

DR. STERN: The same reason you treated your mice at 30 times the milligrams per kilogram recommended in humans.

I guess my comment would be there are things you'd like to know and things that you can reasonably expect to know from both clinical trials and particularly

from post-marketing surveillance, and given the population treated, which has a naturally higher risk of psoriatic arthritis and has some other risk factors for osteoarthritis, if you look at the body mass index of these individuals, it's higher than the average. I think you'd like to know that but will never know it.

However, I think the second part that you allude to, if in fact there is good post-marketing surveillance, there are some adverse events that are not unique in any way to psoriasis that are important, demonstrable, and if you really have good follow-up, you can see if there's an excess incidence of demyelinating conditions, MS, lupus-like conditions, which you don't expect to occur in higher rates than in the general population and, if you have a sufficiently powered study, would give you an indirect index.

But sure, I'd like to know if it makes arthritis worse, but if you haven't detected it in these studies, I think anything can be found out, but I don't think it should be one of your 10 highest priorities.

DR. KATZ: My answer to 4(a) would be it does not raise great concern, but I certainly would have it in the labeling, if the drug is approved, because if does it at, as was mentioned by Dr. Weiss, 2 milligrams per kilo, 1 milligram per kilo is not very far from that. So I would

certainly mention it.

DR. SAWADA: I have a question for the company. Just a point of clarification. Did you not mention that you were doing some studies with this medication in psoriatic arthritis? Was I wrong in remembering that?

DR. JOHNSON: Yes. Our partner Xoma are, in fact, conducting a trial in psoriatic arthritis which is now fully recruited but not completed in terms of the observation period.

DR. SAWADA: So at this time, I wouldn't have a major concern about this. I would just again keep that issue in mind.

DR. MORISON: Nothing further to add.

DR. BLAUVELT: Similar.

DR. DRAKE: Nothing new to add.

MS. KNUDSON: It just makes me very convinced that we need follow-up data for a long period of time.

DR. TAN: Not much new to add. I really think this just should be reported in the label.

DR. RINGEL: I think it's very difficult to get a handle on these low incidence serious adverse events. I think having a phase IV study obviously makes sense. I think trying to beat on physicians to fill out the MedWatch forms would probably make a lot of sense. The other thing we could do is try to get this drug approved in a country

with mandatory reporting, such as Norway, and then look and see what they've done.

(Laughter.)

DR. STERN: I think in Norway, you'd have a power problem. There aren't enough people.

So we'll go on to the fifth question on thrombocytopenia. Thrombocytopenia that was consistent with an immunologically-mediated mechanism occurred in a small number of Raptiva-treated patients. Overall, 8 patients experienced platelet counts of less than 50,000, a grade 3 NCR adverse event; 5 were hospitalized and treated with steroids for their thrombocytopenia. Raptiva was discontinued.

There are four related questions to this.

Do these data indicate an association between Raptiva and thrombocytopenia?

Should the company be asked to obtain additional data to more fully characterize this risk?

Please discuss whether the data are sufficient to allow recommendations on the management of this risk?

Is it appropriate to recommend that patients be monitored for thrombocytopenia if Raptiva is approved for marketing? And I'll add mine. How often and when?

Let's see. Dr. Ringel?

DR. RINGEL: I think that the data are very

suspicious for an association between efalizumab and thrombocytopenia. It's not definitive but it's certainly worrisome. Yes, the company should be asked to obtain additional data and that would be in phase IV studies, of course, and also studying the anti-platelet antibody responses.

I'd say that you're taking me back to basic science here. As I recall, it takes about a month for platelets to regenerate. So that means that if we really wanted to catch all of the people who are going to crash, we would need to monitor them once a month, basically. That's what you do with methotrexate, but I think the problems with methotrexate, the incidence of methotrexate, neutropenia and whatnot, are much higher.

I don't know. It's sort of going out on a limb. I'd say that once a month at the beginning and then as we gather more data, we could probably cut back on that, and I guess that's about it.

DR. TAN: Yes. For the first, I would say no. The data doesn't suggest association.

The second one would be yes. More data to categorize this risk. Those data would be helpful to the management of this risk.

The last one is yes.

MS. KNUDSON: I'll pass.

DR. DRAKE: I have a question. I remember your presentation, Dr. Papadopoulos, that she couldn't remember why the C-reactive protein -- she didn't have a good explanation for why these lab things happened. Is that correct? Since I've already missed one thing the company said already today, do you guys have anything to add to that? I want to follow up on this lab stuff a little bit. Do you have any explanation for why these things happened?

DR. JOHNSON: So one thing we do note is that at baseline, both the placebo- and the active-treated patients have a higher CRP than the normal population. Whether that's due to the chronic inflammatory nature of the disease is probably true. We do not have any explanation -- and Dr. Krueger sort of went through this earlier -- about whether the CRPs are elevated or not. It's only a relatively small proportion of patients who drive the mean up. So it's not a general trend amongst all patients.

DR. STERN: That last comment, I guess I missed in reading the data. What proportion of individuals have a doubling? As I remember, the overall effect was about 25 percent increase among treated patients.

DR. JOHNSON: Yes, right.

DR. STERN: What proportion of individuals have a doubling of their C-reactive protein?

DR. JOHNSON: So I can tell you that this basically represents the data on that, the C-reactive protein. So compared with 13 percent of placebo patients who had that shift from low normal to very high on day 84 was 13 percent compared with 22 percent in the Raptiva group. So it is a proportion of the patients who have changes.

DR. STERN: Thank you. I think we better keep on going with questions. Does that answer your question? Do you want to make some more comments?

DR. DRAKE: No.

DR. BLAUVELT: As far as the association with thrombocytopenia, I feel the same way about this as I do with the flare discussion, that these are real rare events, but is this a platelet-lowering drug in the majority of patients? I think the answer to that is no. It's not a platelet-lowering drug. It's more of an idiosyncratic response that is real but rare.

So getting down to definitely additional data, I agree. I just sketched out that given what we've heard today, I think you're looking for maybe monitoring suggestions. And I would err on the safe side and my recommendation would be to get a CBC with DIF which includes platelets and a chem 20 profile and a CRP and an ANA once a month for the first 3 months and then every 3

months thereafter, not so much to pick up short-term abnormalities, because there's probably not going to be those seen or at least those would have been picked up in the study, but just to see, if we have those baseline data over more than 1 year of use and having laboratory data every 3 months and at 2 two years out or 3 years out, whether we pick up any new signals. So that's what I would recommend.

DR. MORISON: I would go along with that because I'm just thinking about I treat a lot of patients with methotrexate, how often do I pick up, say, a drop in platelets. Once a year? Yet the guidelines for monitoring CBC in methotrexate patients is everybody is supposed to be having a CBC after a test dose, then 2 weeks later, then a month later. So I don't think you should be any less strict here.

A lot of the patients in this study had abnormal liver function tests. So I agree, we should be looking at that not just in 200 patients over the course of a year but over a larger group of patients because, when you think about it, the number of times you pick it up in methotrexate is not that high. So why should this be any less strict?

DR. SAWADA: I have nothing to add on this, except I do have one question. What if you do run across a

patient who has thrombocytopenia? One of the gentlemen who did the platelet study said that the current antibody platelet survey was not very good. Which one would you recommend that we obtain?

DR. MORISON: I'd get them off the drug, and I would try not to put them on prednisone. It can only make their psoriasis worse.

DR. SAWADA: That's what I would think, but take them off the drug but the antibody they said testing for that is against that platelet. He said that the current assay wasn't that good. So what assay would he recommend?

DR. MORISON: Contact the company.

(Laughter.)

DR. STERN: Yes, please.

DR. WARKENTIN: Well, actually there's a number of issues, if I could just touch on them briefly. I want to reassure people. I agree with the comment that was made by one of the committee members. This is an idiosyncratic reaction that occurs in one in several hundred patients. So it's an infrequent reaction, if in fact it is attributable to the drug, and in general, for infrequent and uncommon reactions, hematologists or other physicians don't monitor for those, unlike methotrexate where it's a predictable dose toxicity and it's important to look for

the drug reaction. Of course, if a formal safety study is done, then to build in some sort of platelet monitoring to get some more information about frequency is very important.

Another comment I don't think was really emphasized is that this is a reversible reaction. All the patients have recovered. All the patients recovered promptly on classic immune therapy. So we actually have some good information on how to manage the condition. So we know quite a bit about the condition because we did have 6 patients with it.

In terms of your question about lab testing, it's a very specialized domain. There's only a handful of laboratories in North America that can do these kinds of studies. You can't just say platelet antibody studies locally. So it's another element to build into a safety assessment, that when future patients are identified, if they're identified, the specialized studies can be done. I don't think I need to tell you the nature of the studies, but there are some specific studies where you mix antibodies, you mix the drug, you add patients, and you look for various signals. So these are studies in defined protocols.

DR. KATZ: Yes. I don't know why you would need special studies. Why wouldn't a platelet count be

good enough?

DR. WARKENTIN: Well, you see, this is in the domain of immunohematology and you look at all the drugs that cause immunohematologic reactions. Heparin and valproic acid and Rheopro, to mention three of them, all have completely different mechanisms, and we know that those drugs cause immune thrombocytopenia because we have tools in the lab that can show the link of the antibody to the drug. So if this is a drug-induced immune thrombocytopenia, immunohematologists will be able to sort that out with the appropriate tests, as has happened in all these other reactions.

DR. KATZ: That would be interesting from an academic standpoint, but from a practical standpoint, the doctor would just --

DR. WARKENTIN: Well, from a practical standpoint, we know that if a patient has thrombocytopenia of that degree, you stop the drug, if they have symptomatic thrombocytopenia, you institute the treatment, et cetera. So we know already the treatment approach. Being able to show it is drug-related versus another cause, that's the importance of having the right test.

DR. KATZ: In answer to the question (a), I would say yes or at least most likely, yes, there's an association. Yes, the company should obtain more data. I

don't see how they would obtain more data except with further follow-up studies with a larger group of patients in phase IV study.

I'll pass on (c) because appropriate treatment by hematologists at that time would be appropriate, I would think.

And should it be appropriate to recommend patients be monitored for thrombocytopenia if the drug is approved? Yes, it should be.

Safety of long-term continuous treatment with thrombocytopenia. I think more patients would have to be treated.

DR. STERN: I think, yes, the data are consistent with the significant association between Raptiva use and thrombocytopenia. My answers for (b) and (d) depend in part on data that I don't think I saw which is not only the time course of these 8 sentinel events relative to treatment but also the time course of changes in platelets relative to treatment because I think one of the ways of being guided in when to test is when in fact the events are most likely to occur. So I'd like to see either that information displayed or that information gathered, depending whether it exists or not.

I have nothing to say about (c).

The one plea I would make, whatever

recommendations there are for testing, I don't believe that the ANA is a useful test because of the high prevalence and instability of the test over time in adult and particularly older adult and female populations. You get so many false-positive results that are transitory of unknown clinical significance, that I think that's not a test that has been helpful to us. It's a test that's indicated if an individual develops pericarditis or a different eruption or an increase in arthritis. It's certainly a useful diagnostic test, but I don't believe as part of routine screening in fact it has good operating characteristics to help one in clinical management.

Were you going to give us data on the time course? That would be helpful.

DR. WARKENTIN: That's a very good question, because obviously if the committee is going to consider the issue of monitoring, they should be aware of slide 5. So, yes. As you can see on the right column, it gives the latency of the platelet count fall, and as you can see, it's not until about 3 or 4 months that the thrombocytopenic events began to occur. The two cases on the bottom are the cases that were considered to be unlikely drug-induced. They had other explanations.

So in terms of the monitoring, there was a suggestion made every month, the first 3 months. Well, in

fact, this type of reaction, if it is drug-related, seems to occur beginning about 3 or 4 months.

DR. MORISON: (Off microphone.)

DR. WARKENTIN: Well, even reviewing all the platelet count data, my best estimate from the data is that the onset is around 3 months is the median and, of course, there is some greater time to detection, but looking at the overall patterns, it's not a reaction like some drugs that occurs after, say, a week, like heparin, or after a month. The association needs to be about 2.5 to 3 months.

DR. MORISON: It would seem to me that reading this, that the patients turn up with bleeding gums and genitourinary bleeding. So that's when people started thinking that they had low platelets. Isn't that correct?

DR. WARKENTIN: Well, actually, this is another comment. There was a comment about 5 of them being hospitalized. In fact, only 3 of the 6 patients had any symptoms at all, and of the 3 that had symptoms, 2 were mild. That's shown on this slide, if I can choose this slide. You see patients 1, 3, and 6 didn't have any bleeding manifestations. It was spotted by one of the sponsor platelet counts, and the other 3 had bleeding, of which 1 was a patient with perianal psoriasis who had some rectal bleeding which he'd had several times even before the thrombocytopenia began, and 1 had bleeding with cuts.

So really, to try to mitigate the reaction or to try to put it in some context, it was only 1 of the 6 patients that had clinically significant bleeding with genitourinary hemorrhage. Not to underscore that reaction. The patient was hospitalized, had therapies.

I think one of the important things is, remember, the physicians had no idea what the thrombocytopenia was about. This was a research study. We now have a reasonable picture emerging that it appears to be immune, stopping the drug, and if the symptoms are warranted, it's reasonable to commence treatment. That puts physicians a lot further ahead now in terms of having an appropriate response to that issue, but actually only 1 of the 6 patients had significant symptomatic thrombocytopenia.

DR. MORISON: When were those platelet counts done? 84 days?

DR. WARKENTIN: It varied from studies, but one was generally done at 84 days. That one was generally normal. It was generally the subsequent platelet count or counts that were lower.

DR. PAPADOPOULOS: I had the same comment, that in study 2600, they were done at 84 days and not prior to that. So I just wanted to clarify that.

DR. STERN: Those of us who are simple

clinicians think that it takes awhile to get from 250,000 to 3,000, and we'd rather find out as it's passing below 6 digits into 5 digits rather than when it gets down to 4 digits. So I think in fact if that's all the data we have, we need some fairly robust information about what's happening perhaps at 4 and 8 weeks to see whether we can spot things when they're still in the low 6 digits or the upper 5's and not below 30,000 which is the kind of platelet count that at least as a non-hematologist makes me very nervous.

DR. EPPS: Well, it certainly suggests an association. It would be nice if the company or FDA or whomever, when someone has a drop in platelets, should specific tests be obtained? Should specific things be looked at to further characterize the patient? Quite a few of the patients were on other medications, including aspirin, and some other things. Could that have an effect as well? Although 2 of them were on no medications at all.

I agree with waiting if you're going to monitor the platelets. Most of them were 3 months or higher. It would have been nice if all that had been discussed this morning when we were talking about thrombocytopenia.

Also, monitoring, I do think that's appropriate post-marketing, and I guess some labeling comment could be made but that's correct. I mean, the fact that some people

were not symptomatic is even more worrisome actually. I'd like to have an indication before somebody drops down to 16 or 3,000 platelets, if they don't have any symptoms. That's of a lot of concern. I'd rather know about it than not know about it.

DR. SCHMIDT: I have nothing really to add, except that in that group of people who had the thrombocytopenia, some of them were on anywhere from 7 to 8 medications, and the one who wasn't on any medications had had a ruptured aortic aneurysm, and then there was an alcoholic and somebody on methadone. So I think there's also some other reasons that you would monitor somebody like that.

DR. SIEGEL: I think when Dr. Drake was starting to answer, she started to talk about some of the other laboratories and never gave us her thoughts on the thrombocytopenia or monitoring. I wonder if you had more you wanted to say about that?

DR. DRAKE: I got sidetracked, didn't I? I figured I had taken up my time at the mike and it was time for me to stop.

I agree with Rob. I have grave concerns about missing something. I mean, our goal is to have something that's efficacious which I think this clearly is and I really want it to get to the patients.

On the other hand, if something's gone haywire, I want to know about it. I don't want to wait till their platelet count is 3,000. I'm going to be in the middle of the night trying to run around down a friendly hematologist in an absolute panic because that's the type of patient who will show up in your office at 5:30 on a Friday night. I would just far prefer to know that at least if there's something that's going to alert me, I want to be alerted early so I can deal with it.

There are some patients that this probably just isn't going to work for and it's nice to identify them early so that you get them off that drug and onto something else. It's going to be a tiny percent and that's true with all drugs. If you think about it, we do this with all. Like Warwick said, there are not so many people on methotrexate that you have to stop, but jeepers, if it's your mama that is that one patient, you sure want it stopped right then.

So I would just prefer to know sooner rather than later, particularly since this is a whole new class of drugs, since we're early in it, we only have 200 patients in the long-term, I would just have a greater comfort level, at least for awhile, with a little more frequent monitoring.

Did that answer your question?

DR. SIEGEL: Yes.

DR. STERN: Dr. Weiss?

DR. WEISS: Yes. I just had a question. I think Dr. Morison said something that made me wonder. Usually if there's an adverse event, a label will recommend appropriate action. Oftentimes it isn't too directive on the type of management of events, leaving it to the experts or the consultants, such as a hematologist.

In this particular case, since steroids, prednisone is the mainstay of treating autoimmune thrombocytopenia, and Dr. Morison raised the concern about don't treat them with prednisone because it'll have some effect, maybe make their psoriasis worse because usually the treatment is a course of steroids, then a taper-down over a month of a higher dose and then tapering down.

So is there a specific concern? In a population that's not a psoriatic population, steroids would be the mainstay of treatment. Should there be some more specific directive in terms of how to manage?

DR. MORISON: I don't even know whether you would call it directive, but I think that finding out the platelet count is low at the earliest possible time so you can avoid prednisone therapy is by far and away the best idea because in my experience, people on prednisone run a high risk, when they come off prednisone, of developing

erythrodermic or pustular psoriasis. So you want to avoid particularly high-dose prednisone, and the dose I heard this morning, the patient was back on prednisone of about 300 milligrams a day.

DR. WEISS: It was actually 5 milligrams a day, not 500 milligrams per kilogram a day.

DR. MORISON: Oh, okay.

DR. WEISS: It was down to the tapering maintenance.

DR. MORISON: It would be wonderful for their psoriasis for a short period of time.

(Laughter.)

DR. WEISS: But if a patient does need to be treated, I mean there are other things.

DR. MORISON: If they have to be treated. Like a person with psoriasis who has an enormous outbreak of poison ivy, you've got to treat them, but you want to avoid it if at all possible.

DR. DRAKE: Can I make an additional comment? This is always a dilemma. Do you mandate it or do you recommend it? I don't know the answer to that. I have a strong bias against mandating to clinicians how they take care of their patients because I think good doctors do a good job. So when I spoke to say I think more frequent monitoring is advisable, that's my personal opinion and my

comfort zone.

Whether you mandate it or not, I think, is another issue. You asked me how strong to put it in there. I don't know. I might use something like strongly encouraged because what you don't want to do is to have somebody who's doing great, who's self-pay, who's doing just fine -- it's just very hard. So I have a little bit of a problem with mandating versus strongly recommending, if that is of any help.

DR. STERN: To take one step on Lynn's point, at least for some agents labeled for psoriasis, there's a specific recommendation that they only be used by people who are -- I've forgotten the exact words -- expert or experienced in the care of patients with psoriasis.

Basically, I think what we're hearing is this is not a straightforward agent to use and it is complicated by the difficulty in managing the appropriate patients with this disease that takes a lot of experience and a lot of knowledge about the options. So perhaps part of the labeling should be analogous to what it is for some other products for this or similar indications as opposed to mandating that says this is not something that someone who sees someone with psoriasis and isn't experienced in the broad range of options should be really thinking about prescribing because there's too big a chance you'll either

forget what to look for or get in over your head when you try to withdraw the therapy.

DR. DRAKE: I think another thing, if you're talking about recommendations, this is kind of aside, but I think this panel could probably make strong recommendations to the sponsor that if this is approved, that they certainly embark upon a massive educational and informational effort to the practitioners so that they have a clear understanding of this. I mean I think that's an essential recommendation that should come out of this group.

DR. STERN: I think we'll move on to the real question 6 now, the overall risk-benefit and patient population. This is only a two-part question.

Based on the existing safety and efficacy information, please discuss which populations of patients may be the most appropriate for use of this product.

The sponsor has proposed that the indicated population be "adult patients with moderate to severe plaque psoriasis." Eligibility criteria permitted enrollment of individuals who had prior systemic therapy or phototherapy as well as those naive to such prior therapies. The entry criteria excluded patients who did not have chronic, that is diagnosed for at least 6 months, plaque psoriasis at baseline. Patients who were not

clinically stable for at least 3 months were also excluded.

The two questions for our opinion is, should the use of Raptiva be limited to patients who have failed or had an inadequate response to phototherapy or systemic therapy? And the second is, should the use of Raptiva be limited to patients with moderate to severe plaque psoriasis who have stable chronic disease?

DR. SCHMIDT: Yes and yes.

DR. EPPS: Yes and yes.

DR. STERN: Yes. We're talking about risk-benefit. Even though the majority of the populations treated were severe psoriasis, is it better to label a product like this until we have more information for the group that is most likely, based on severity of disease, to have the most potential benefit, not in the statistical sense, but in a sense of the benefit.

One generally feels if you make a severe person better, you've done more for that person. So I just wonder if the more conservative thing would be should the use be limited to patients with severe stable plaque psoriasis. Just a thought.

DR. KATZ: I think the wording might be too restrictive because inadequate response to phototherapy -- there may be people in whom that's not feasible. So you're limiting somebody in that way. Or systemic therapy. I

think that's not properly worded because there might be some people who are not candidates for other systemic therapy. So I have a problem with that.

(b), it should be limited to people with moderate to severe plaque psoriasis. The answer there is yes.

DR. SAWADA: For me, (a) is yes and (b) is yes.

DR. MORISON: I think yes and yes.

DR. BLAUVELT: I strongly believe no and no. I think that here you're getting into dictation of clinical practice and I don't think that we should go there. I think on an individual patient who may have liver disease due to whatever, hepatitis C, or can't take cyclosporine, I think the physician and the patient, after going through all of the options available to that individual patient, should be allowed to make the choice between the two of them that this may be the best drug for that particular patient.

I feel very strongly about that. I don't think we have to push people to methotrexate and cyclosporine or light therapy if they want to use Raptiva and can afford it. I also have a personal family history of psoriasis, and if I were to get the disease which I'm susceptible to, I would perhaps use this as my first drug. Just knowing what I know about methotrexate and cyclosporine and light

therapy, I would rather take this as the very first drug if I needed systemic therapy. That's just again my personal opinion, but I feel strongly about not making the choice of the clinician, not taking the decision out of the clinician's hands.

And (b), I'd say is no, because this may work beautifully in pustular psoriasis or erythrodermic psoriasis, but we have no data. So why limit a doctor who has an erythrodermic patient who wants to try Raptiva? I know there's no data on that, but it's an approved drug for psoriasis. It may work beautifully. We don't know.

DR. WALTON: Just to clarify what we meant by that because I'm not quite sure if I understand your answer. In that (b) question, when we say limited to, we don't mean restricted only to. What we meant was a statement of indication as to who it's indicated for.

DR. BLAUVELT: Yes. That's the answer.

DR. WALTON: But it obviously does not restrict practice of medicine. So I guess my question then is, are you saying that the indicated population should bear no comments on --

DR. BLAUVELT: No, I'm not saying that.

DR. WALTON: -- who is selected?

DR. BLAUVELT: I'm not saying that.

DR. WALTON: Okay.

DR. BLAUVELT: The word "limited," I guess I was interpreting differently.

DR. WALTON: Right. We did not mean limited in the sense of you may never use it in anybody else. We meant it in the sense of who it should be described as the indicated population.

DR. STERN: Could I have your position, Andy, again on (a) and (b)?

DR. BLAUVELT: So (a) would be no and (b) would be yes.

DR. STERN: Might I make a suggestion for some wordsmithing for (a) to put in that one should consider options? Actually what I'm most comfortable with is something along the lines of that Raptiva should be limited to patients who have failed or have had an inadequate response or for whom the therapy was either not tolerated or is inappropriate and other systemic therapies.

DR. DRAKE: I disagree with that.

DR. BLAUVELT: I'd still say no on that.

DR. DRAKE: I'm with Andy. I strongly, strongly, strongly say no to (a) because I know for a fact that with methotrexate, I've got worry about their liver, and I know for a fact with cyclosporine, I've got to worry about their kidney. I mean this may just be something I don't have to worry about much of anything, except

something later on that's minor and can be dealt with. All right. This may be end up being the first best choice for systemic. I know with PUVA, we get skin cancer.

I mean, I'm not saying none of those things will happen with this, but this may ultimately be what I want to use first. So I would strongly say no to that because it's just wrong to try to dictate which one might be best for the patient, and this might end up being the safest of all. So I just want to say strongly no on that one.

Then on (b), I think your recommendation to say that the primary target is moderate to severe plaque psoriasis is fine, but again you may find that this works on other types of psoriasis. So I guess my answer on (b) is maybe.

DR. WALTON: On (b), the emphasis is also on the modifiers of stable chronic.

DR. DRAKE: We've gotten sidetracked a little bit, and I understand your question and it's very good, and I may be wrong on this. So I'm admitting this way up front. But I think I've gotten sidetracked a little bit earlier on by these patients who it's been suggested that perhaps it was the unstable ones who had more likelihood to have a serious AE. I don't think we know that yet, and so maybe they don't have to be stable. Maybe somebody who

comes in with an acute flare of psoriasis -- I don't think the data is there to suggest that we can't treat an acute flare. The study showed it was chronic.

DR. MORISON: I think that's what I said.

DR. DRAKE: I'm not disagreeing.

DR. WALTON: May I clarify?

DR. DRAKE: I'm not disagreeing with you.

DR. WALTON: May I clarify what this question is setting up for?

DR. DRAKE: Okay. sure.

DR. WALTON: This question is setting up a concept of a population to think of as an indicated population.

DR. DRAKE: Absolutely, because that's what we have the data in.

DR. WALTON: Right. For which you can subsequently comment on whether you think the efficacy that we can expect in that population outweighs the risks.

DR. DRAKE: Yes, I think that's absolutely true, because that's clearly what we have the data in, is this population.

DR. BLAUVELT: But the word "limited."

DR. WALTON: Please do not misinterpret the word "limited." We are not talking about a contraindicated in all others kind of thing. We're thinking of a statement

in the indications section that might describe who the drug is indicated for, bearing in mind that the practice of medicine by any individual physician is to use their best judgment.

DR. DRAKE: I still say no to (a) in view of everything you've said for the reasons I outlined. (b), I'm not sure. I think I would say yes to the first part of that, take out the word "limited," but indicated for patients with moderate to severe plaque psoriasis. I'm not sure we've proven the case for stable chronic disease.

DR. STERN: Might I remind the panel that as I recall, the evidence base we have is almost exclusively in patients who have had their disease stable over a number of months period of time before they began the treatment, and if I'm wrong about that, but that's what I recall was the evidence base. And I've always thought that the label is supposed to be evidence-based.

DR. WALTON: The label is supposed to be evidence-based but, of course, we can never indicate it solely for the populations studied, and so we rely upon your judgment to help guide us in how wide or how narrow to extrapolate and to generalize.

DR. PAPADOPOULOS: I have another comment, just again for clarification. I said this before. The first two studies required the 3-month period that the patient be

stable, and in study 2390, I'm looking for the specific wording. There was an exclusion criterion.

DR. WALTON: I think the general sense is that in some of the earlier studies, there were specific requirements for stable periods. In the later studies, there were an avoidance of patients who were unstable. Whether you want to interpret that being identical or not, I think is a matter of judgment.

DR. DRAKE: One of my problems is, as a clinical investigator in looking at this, it's very, very tough to define stable. I don't know of any psoriatics who are necessarily stable. So maybe that's what my problem hinges on. You do the best you can to find somebody that's sort of been semi-stable, but it's hard to find somebody with psoriasis who's real stable, unless they're just an old burned-out psoriasis who have given up on everything. But somebody who's kind of in active disease or new disease who might be best served by something like this, I think it's hard to define stable.

But I have no trouble with using that language because that's the basis upon which -- as Rob so rightly pointed out, that's the evidence. So I have no problem with you using that.

DR. STERN: I guess I would say one thing from clinical experience, that things that work modestly often

for stable plaque psoriasis work less often for unstable psoriasis as a general rule in clinical experience, and I see even Dr. Krueger shaking his head with that.

So I think perhaps before we go beyond that, it's useful, if people wanted an expanded indication, we'd really like evidence that the results would be at least as good in a population of people with other forms or unstable psoriasis because, as you point out, we're supposed to give you our clinical and other experience and use this to interpret the data. Certainly if you ask me if it works this often for this population as treated, what are the chances it's going to work in erythrodermics and pustular psoriasis and people having rapid flares? My experience says that there's usually an association in the efficacy level between one and the other with the efficacy being lower in the harder cases.

DR. BLAUVELT: Can I change my answer after that discussion?

(Laughter.)

DR. BLAUVELT: So I end up saying no and yes. I would say no and no now because in my opinion, after the discussion, I don't like the word "stable" in the indication. Even though that's where the data is and that's how the studies were done, I think if that word "stable" is in the indication, I think that will limit. If

a doctor has a patient sitting in front of them who's getting worse and, well, I can't use this drug because you are not stable, I don't want that to happen.

So I think I would prefer, even though I know that's where the data was but that's how clinical studies have to be done -- I would argue for a label that just says for moderate to severe chronic plaque psoriasis and take out the word "stable."

DR. DRAKE: I'm back with him.

(Laughter.)

MS. KNUDSON: I will say no to (a) as well because I do think individual patient-physician decision making is paramount. And I would say yes to (b) because that is indeed where the studies have been done.

DR. TAN: I will say no to the first because someday you may find this is exactly the patient we should treat first with.

For the second one, I think that the "stable" -- I look at study 2390 and that's a 6-month definition. There's another one that's a 3-month definition of stable. I think that is the range in the data. So, therefore, the "stable" in this you can extrapolate is to 3 months. I would like to have at least some kind of criterion there, maybe one week or one month. Maybe it's not just one day.

DR. RINGEL: I like the word "stable." I think

it's a nice word. So I would say yes to part (b).

I'm an unusual person to ask the first one to because I don't like using any new drug before it's been out for a couple of years, unless there's a good reason that I should. The patient isn't responding to other things that are on the market. There are too many things that have gone wrong with the new drugs, and if there are other things available, I like using them first. I think that just makes sense.

However, I guess my problem with it is Alefacept. If I recall, that was a very similar drug that had been approved simply for patients who were candidates for phototherapy and systemic therapy. I don't know how we turn around to this company and say with no real reason, well, yours should be more restricted than theirs, and I don't know what to do about that. So I guess I'm going to kind of vote no on that one, although with some trepidation.

DR. WALTON: Dr. Stern, in thinking back over the answers that we've heard, a number of the people have discussed their answers, and I think we understand the answers from the people that have discussed it. A number of the people were much more concise and really did not discuss their thinking, and in looking at this, I noticed there's a difference in the way they answered it, that I

think it would help us to understand their thinking better, in that for the (b) part, many people went along with advising that the FDA ought not to generalize too far from the population study.

But for the (a) part, the advice from some people is that we ought to narrow from the population studied in that the population studied included both those that had previously received the systemic therapy and phototherapy, as well as patients who had not previously received those therapies. Yet, some people advised that we ought to have the indicated population as only those who have failed or are otherwise inappropriate for those. So it's a narrower restriction.

I wonder if you could go around and ask for some discussion of their thinking on that.

DR. STERN: If I may take the chair's liberty of starting with my own logic, and it goes back to the slides I showed about 8 or 9 hours ago which in fact showed the now-labeled indications for a group of drugs that are used as systemic therapies for psoriasis which each have their benefits and their risks. When I look at those indications, if you were simply a clinician being directed by those labels, I think what Dr. Ringel said is exactly right. Your automatic first choice, based on the indications section, would be that you should automatically

go to Amevive, Alefacept, first, because it looks so much less restricted as an indication.

I guess my plea would be perhaps that in looking at the class of drugs, I myself think that one cannot distinguish very accurately in terms of risk-benefit among the class and that the information should be there, so that quite frankly, as has happened to me, the detail person can't come around and say, thinking I am the naive recipient of this information, well, look, don't use methotrexate or PUVA anymore because look at what their label says and our label just says, no problem, Charlie.

So to me, it's really having a level playing field among agents that have either documented risk or potential risk for a similar indication and what would be most useful to the clinician, and I hope everyone would agree that if all of these labels were in some way consistent so the doctor could make the informed choice without being, really in a certain sense, in the court of law. If I use methotrexate before Amevive now and the patient has an adverse event, if I were a good lawyer, I'd bring it up and say, Doctor, look here, this drug doesn't say anything about all these limitations. Why didn't you use that first?

So that was my plea, that look at not just the biologics but the systemic therapies, look at their labels

in terms of indications, and look at what we know about their side effects and the groups in which they've been proven to work, and give a balanced representation across. There are only about five or six of them out there. So it's not like redoing topical steroids or nonsteroidal anti-inflammatories. So give us a balance that reflects it.

So as sort of Andy says, the clinician can, in reading the label, not be swayed by, what I say, the detail man, and what Andy said in the positive way, be able to really consider this is the information base and if I look at these, the label tells me about the important known and unknown things about efficacy and about concerns about safety for each one.

I'm sorry. I digressed too much.

DR. WALTON: No, no, no. A full explanation of your thought is really very important to us.

If I can interpret it in a little concise form, though, or a bit of it, if I understand what you're saying, though, is you're not concerned that this product should be recommended solely as sort of third-line therapy, that is, after topicals and after systemic or phototherapy only, but rather that it should be a balance in keeping with some of the other systemic or phototherapy sorts of treatments.

DR. STERN: Yes. Taking away what you said, if

you think topicals are going to work, I always think they should be used, if practical, before.

DR. WALTON: Right.

DR. STERN: But I think the label should be written for the group that there's an evidence base for, in my mind synthesizing this in a way that gives one a similar comfort or discomfort level, depending whether you're looking half full or half empty, as the other systemic therapies. Obviously for each one, there are different concerns and there are different populations where efficacy has been proven, so you'll have to modify that according to that.

But in terms of the overall flavor, I can't easily distinguish upon this drug with a very short long-term safety record and certain concerns and other drugs that are other systemic therapies. So I'd like the flavor with the specificity to be there in terms of the evidence base of who it's really been tested in, but the flavor of the indication to be similar among those class of agents.

DR. WALTON: But not necessarily putting this one behind the others.

DR. STERN: No, no. But not implicitly ahead of the other established therapies.

DR. WALTON: Okay. I would appreciate hearing some of the thinking from the other people as well.

DR. STERN: Yes, please. I'm sorry.

DR. SCHMIDT: I go along with the chef's concept, too, about the flavoring, and I agree that these older medications, we do know the side effects, and we know what we're doing. In a sense, this is a new therapy and to put it on this level playing field where you're not going to be swayed but not necessarily put it as a third-class-citizen-type thing, that's how I feel, too. So I still say yes.

DR. EPPS: I guess my basis was on the studies that were performed and the data that we were presented with. It may work for other indications. There may be compassionate use, but this is who we studied, the people who failed therapy or who had previous systemic therapy and the ones who with "stable and chronic" disease. Correct?

DR. WALTON: Yes, but there were also patients who were naive, who had not received the systemic therapies or phototherapies. Such patients were studied and included in the studies as well.

DR. EPPS: I'm sorry. Which study was it? Do you remember the number? All of them? They were sprinkled through?

DR. STERN: They were about half the population or about 40-45 percent of the patients.

DR. EPPS: But even still, there's limited

data, in my opinion. That's my opinion. I mean there's a small population that really benefitted from it compared to some of the others. We have more experience with methotrexate. We have more experience with cyclosporine. We have more experience with other systemic agents, and that's just my opinion. I would wait.

DR. KATZ: I think I stated it before. Some people may not be able to go for phototherapy or may have reasons not to use systemic therapy. So this is limiting that. But if it could, say, in some way limit it to patients who are candidates for other systemic therapy, for systemic therapy or phototherapy.

DR. WALTON: Again, going to the concept I tossed out about the idea of equal footing for placing it to be used after the others were considered, you're suggesting it is a product that should be more on equal footing or it should be more --

DR. KATZ: No, not equal footing. If I used it, it would be the last thing that I used, especially since 100 patients have used it for 1 year, only 100 patients.

DR. WALTON: Okay.

DR. KATZ: But that's my personal answer. It certainly should be used with that safety data and what we know restricted to patients requiring more than topical

therapy.

DR. WALTON: Okay.

DR. KATZ: Perhaps the same wording as Amevive. What wording did we have for Amevive?

DR. STERN: It was very liberal.

DR. BLAUVELT: So his answer is changing from yes to no.

DR. KATZ: No. My answer first wasn't yes. My answer was that this --

DR. BLAUVELT: Oh, right. You're right. I'm sorry.

DR. KATZ: -- may not be available. My answer to (b) was yes. My answer to (a) was you're restricting somebody.

DR. BLAUVELT: Right.

DR. KATZ: If somebody using it gets into trouble, then maybe it wasn't indicated. Maybe the patient couldn't get to the office for phototherapy or had some reason not to use methotrexate. So this is restricted.

DR. WALTON: Right. I understand. You're saying that you don't want to restrict it solely to those who have actually tried, but yet in your mind, you would still --

DR. KATZ: To restrict it to patients in whom those would be indicated.

DR. WALTON: Okay. I think I understand your thinking.

DR. KATZ: Sufficient severity of psoriasis to require more than topical therapy.

DR. SAWADA: I guess it seems like everything is stuck on the word "limited." I think in the discussion that's ongoing, I would have to say I would agree perhaps not to use the word "limited." So I would say no and yes would be my answer, changing my answer to (a).

This is where I probably would use the art of medicine. It's a label that indicates use in, but quite frankly, if I had a patient and after discussing all this with them and between the two of us, we came up with the idea that perhaps this is worth trying in them, I wouldn't keep this from stopping me from using the medication. Again, right now, it's kind of a verbiage thing, but I can see where the word "limited" would maybe stop someone in their tracks.

DR. WALTON: Again, perhaps our questions were not well phrased. By limited, we really meant indicated in and we didn't mean restricted only for use in.

DR. STERN: I think the terminology clinicians are more used to is "indicated for the treatment of X" and we know that there's a lot of off-label use. So perhaps just changing that to "indicated" might be better.

DR. WALTON: Yes. It would have been better if we had phrased the question that way.

DR. EPPS: Or recommended for.

DR. MORISON: My reason behind saying yes and yes was that after hearing all the information this morning and this afternoon, I don't feel as comfortable with this agent as I do with Amevive. And the reason I don't feel as comfortable is because the number of patients that have been followed is smaller, the duration of follow-up is smaller, and I think there are more loose ends with this particular agent.

So for that reason, I'm happy to go along with is indicated in patients who have failed or have had an inadequate response to phototherapy orother systemic therapies, or if these were contraindicated or unavailable. I'd be perfectly happy to go along with that because the next question was would I use it. Yes, I would use it in those circumstances on the basis of the data we've been given.

DR. WALTON: I think the people on that side have already discussed their thinking well.

DR. STERN: Now we come to the denouement of the whole day which is the basic question which is one that we want a formal vote for, which is, in light of the above discussions as to which patients may be most appropriate

for use of Raptiva, is the overall risk-benefit comparison for use of Raptiva favorable?

May I ask if this means you've heard all of the opinions about in whom, what qualifications, what recommended, taken all of that and assuming that you in your wisdom will use that advice as part of your decision making, basically this is the global. Now we've talked about the individual things. With all that as taken, is it yes or no for this agent?

DR. WALTON: Yes. I think at this point, we've gotten some very good discussion on lots of different aspects of efficacy, of safety, of population selection, and if somebody felt that there was something they had not already said, then we'd like to hear it, but otherwise, I think that this really is coming down to a very simple yes/no.

DR. STERN: And you understand that the members of the committee have to take that vote on faith that you've been listening to all the qualifications, reservations, et cetera, et cetera.

DR. WALTON: We've worked for quite some number of months to get here to be able to have this discussion. I think you may feel guaranteed we are listening very closely.

DR. SCHMIDT: Yes.

DR. EPPS: Yes.

DR. STERN: Yes.

DR. KATZ: Could I just ask one thing of the FDA?

(Laughter.)

DR. KATZ: On page 4, it says the minimal ICH recommendations to safety database be at 100 patients for at least 12 months. Now, is that for any drug or is that for cancer drugs?

DR. WALTON: No. Those ICH recommendations are for treatment of chronic diseases that are not serious or life-threatening. Those are general recommendations about the minimal safety base that should be obtained in order to begin evaluating safety. It is sort of a guideline towards how much data provides us a reasonable chance of picking up events that might be important in that kind of a clinical setting, and clearly the safety base that they have provided for us here does meet those ICH guidelines.

It is not restrictive in the sense of stating that larger safety databases are never needed. That's a safety database size that permits us to begin to examine, and if we should find something in there that is concerning, additional data might be warranted.

DR. KATZ: Well, assuming that, that's reassuring, but my yes would be very qualified. It would

be qualified so before anybody says that they would prefer to use this as a first drug, we must emphasize only 1 out of 5 patients got a PASI 75, which is a gold standard. Only 13 percent without placebo got 90 percent better. 13 percent. So we've got to treat all those patients with a drug that probably costs at least $1,000 a shot for 12 weeks. With 4 less than 75 percent PASI.

Also, the emphasis has been on longer-term follow-up. We'll have to see. Well, when do we get longer-term follow-up? We have to get it in phase IV rather than phase III. So I would favor continuing this before approval. But in view of the accepted 100 patients and they have 213, I give a qualified yes.

DR. WALTON: Again, the ICH guidelines are not a mandate for what is sufficient. It is a guideline for what is a good basis to begin, and if concerns were raised, one can always feel more is necessary. So we're here now with asking for judgment on that, whether we have sufficient to form a risk-benefit assessment.

DR. SAWADA: Yes.

DR. MORISON: Yes.

DR. BLAUVELT: Yes.

DR. DRAKE: Yes.

MS. KNUDSON: Yes.

DR. TAN: Yes.

DR. RINGEL: Yes.

DR. STERN: The next is a question about studies in pediatric populations, a two-part question. If it is determined that Raptiva is safe and effective for use in adults, please discuss the following issues. Should Raptiva be studied in pediatric patients with psoriasis? If so, please discuss the optimal timing of such studies relative to accumulation of additional post-marketing safety data in adults.

The second part of the question is, what additional studies should be carried out in pediatric patients to fully assess safety and efficacy? Please include in your discussion the potential for loss of response to recall antigens and the potential for impact on response to childhood vaccines.

I would add as a third, when one speaks about pediatric patients as the sponsor did, please define that with respect to what age groups you might have recommendations for as with this type of agent. It may very well vary between, for example, under 12 and 12 to 18.

DR. EPPS: Well, I'll start then since I see things through the pediatric prism. If it's established to be safe and effective in adults, then yes, you could test it, but obviously there are more studies that need to be done. A lot children tend to have guttate. That

population was excluded in the studies. So I would see how that responds in adults and then study in kids.

I would start over age 12 perhaps first. I don't know that I would dip down early quickly. Most of the childhood immunizations are done. They probably have boosters. 12 is kind of a good age to go down to.

Yes, you'd want to monitor antigens. As I said, most of the childhood vaccines are done and certainly I guess it's all dependent upon the adult long-term studies, whether you'd want to try it in children. Yes.

DR. WEISS: Do you have some thoughts, though, about how much -- we've had a lot of advice about additional post-marketing and collecting long-term data and, of course, that can be ongoing for a good number of years. Some of the information, like malignancies, you may not know, if ever, for 5 years or so. So you're not going to have answers to maybe everything that you'd like.

Where would you think, in terms of post-marketing, if this was marketed and licensed for adult use, would be good for initiating?

DR. EPPS: Well, I don't think there's a hurry. I think you can take your time. Also, a lot of young people who are adult size, so if you're concerned about weight, you could maybe start with a weight issue, certain number of kilograms, if you want, over the age of 12. Or

you did go to 18. I don't know how many 18-year-olds or teenagers were included, but certainly that's a good place to start, too, since there is that low peak when that bimodal distribution first rises anyway.

DR. SCHMIDT: I would like to defer to Dr. Epps. Pediatric dermatology is such a specialized field, and I would say over 12 to do some of these studies. But then as far as doing studies on smaller children, I think I'd be real careful because like you say, most of the children have the guttate psoriasis. Then I don't see a lot of real severe psoriasis in children, but when you do, it can really be difficult and devastating to treat. But I think I'd still be really careful with this.

As far as loss of the recall antigens and the childhood vaccines, that's another thing that I don't know exactly what you could do or should do with this, but that's something to really pay attention to.

DR. STERN: If I misinterpreted the statements by the sponsor, I heard some substantial concerns about the potential in the developing immune system for using this drug. And certainly through age 12 and I guess for all the reasons that have been stated, I wouldn't be in very much of a hurry to develop it, even in the next age group, until we had a much larger safety database and also indications that it worked in fact in the most unmanageable forms of

psoriasis in adults.

So to me, there would be both the safety question to be first addressed in adults, then an efficacy question for types of psoriasis that are rare in childhood but extremely difficult to treat, and then it would be starting with teenagers and moving down. And probably in this time period, I think we'll know more about trafficking of T cells with the thymus and how this works better and making sure that we don't get ahead of our concerns about the developing immune system and not getting too low in terms of that.

DR. KATZ: I would wait till more post-marketing studies were done and basically agree with Roselyn Epps and then study it in age 12 and up, and then go to the next group.

DR. SAWADA: I have nothing more to add.

DR. MORISON: I would just add that the need for systemic agents in children is not great. I'm sure we all see an occasional child -- I'm talking about now 6- to 12-year-olds through 15 -- who needs a systemic agent, but that's extremely rare. Most of them can be controlled by something like narrow band phototherapy quite adequately without going to the risk of a systemic agent. I'm just thinking of the last time I used methotrexate, for instance, in an under-16-year-old. It's got to be quite

awhile ago.

DR. BLAUVELT: To me, the operative word here is studied, and I'd say yes, it should be, and now I think is okay, although I agree there's no rush to go into kids, but studied to see what goes on. I think it should be done.

DR. DRAKE: I think it's a little premature to move into children. I'd like to see a little more data in adults. I just think kids are too precious to risk and most children don't die or have serious bad things happen to them from psoriasis. I'm not a pediatric dermatologist, but I used to be the back-up for the ped derm at Emory and it's not such a serious thing. So I would urge prudence and move into it in a timely manner when we have a little more data.

MS. KNUDSON: I would suggest to my IRB that they move extremely slowly, that they have a lot of the phase IV data, safety data and efficacy data, before they ever would consider teenagers and then I would start with 15- to 18-year-olds before I would go to 12.

DR. TAN: Yes. I think the first step may be to just look at the data that is already there, maybe look at the 18-year-olds as a subset. There may be -- I don't know how many -- 18 to 19, to see if there's anything we can watch out for to start with.

DR. RINGEL: I think there are two issues in my mind. One is the response to immunizations in people who are taking the medication and the other is the effect on the immune system. I don't know what has already been done, but I'd certainly want to do studies in animals first, lots of studies in animals first, to see, for example, do the immunizations take in animals and also what is the effect of Raptiva on the developing thymus, this sort of thing. Then at that point, I suppose you could start to do some compassionate use and then follow those patients.

DR. STERN: We'll now move on to the final question which is concerning Raptiva with concomitant systemic anti-psoriasis therapies. In the clinical trials, other systemic immunosuppressants and anti-psoriasis medications were prohibited. If a patient developed a psoriasis-related adverse event requiring alternative systemic therapy, he or she was to immediately stop the study drug.

The question is, please discuss whether Raptiva should be studied in combination with other systemic anti-psoriasis medications, either long-term or for a defined period of overlap.

Lynn, why don't we start with you?

DR. DRAKE: I think with any drug, if you're

having an AE, you stop it, period. I don't care whether it's new or old, just stop it. So I think yes, if somebody is having problems and they're on this, you stop the drug. Then it looks like the life of the stuff is pretty short-lived, and so it seems to me that you wouldn't have much trouble moving into an alternative therapy. Particularly, you could start with topical or light and then move into something more systemic later on.

So should it be studied? Absolutely, because you're going to need it, because you can't just stop this drug. So you're going to have to have some plan in motion to move patients off this drug in any event. So, yes. Maybe I didn't answer your question.

DR. WEISS: I think it's more a question of the fact that there are no data. Is there a role for studies? Not whether or not there's an AE because that's, I guess, a different issue, sort of maybe not a great lead into the question, but really is there a role?

There was some discussion earlier about using rotational therapy as opposed to chronic use and how we don't really know, if you do that, how you would add in something and what you'd add in and for what period of time before you're contemplating stopping this, if you were going to contemplate doing that. Then there are options in many other diseases where you use combination therapies

with sort of non-overlapping types of toxicities.

So I guess the question is really should there be studies that we specifically discuss with the company in terms of post-marketing-type studies to evaluate other types of ways to utilize this?

DR. DRAKE: Well, I think yes, you should discuss it with the company. Should this be a rate-limiting factor in getting this drug out? I don't think so. Now, I may be misspeaking here, but it's been my notion, at least with rotational studies, that tends to get worked out once it's in the marketplace anyway because clinicians will begin to do their own studies, investigator-initiated studies to figure out what rotations work. Warwick is famous for that and so is Rob. There are people around this table who have actually done a lot of this kind of stuff. So I think a lot of the rotational stuff will fall out once the drug is approved and smart docs start looking at it. So I'm not sure that should be mandated.

Now, with respect to the other question then, administration of two drugs at the same time, yes, I think there's a role for that. I think if the company has notions about what drugs might be combined, I think that should be done under really formal study conditions, at least initially.

DR. BLAUVELT: Combination therapy. I agree clinicians are going to be doing that, if this is approved, even though there's no formal study of it. Then I think the anecdotal experience that's gained from the clinical community of combination therapies will then direct the formal studies to show that the combinations are effective or not.

DR. MORISON: I agree. I think the studies are going to be done. The company is probably going to want to initiate them in any case because here you've got a drug which has a rather low efficacy rate and a rapid deterioration rate once you come off the drug. So you're going to need other agents and know how they interact, and the company is going to need to provide that information.

DR. SAWADA: I believe that the practicing clinician will be doing a trial and error type of study on their own and that the company will probably pick up on combinations that might be worthwhile studying.

DR. KATZ: My answer is yes, and I agree, it's going to get done anyway because the drug doesn't work that well in a good portion of the population.

DR. STERN: I guess certainly in terms of combination rotational therapies, I agree that clinical practice will move it on. I still would like to know what to do when I want to get a patient off this drug for that

transition and what to do when a patient in fact is flaring on the drug. At least when I read the evidence presented, I didn't have a good idea about what were likely to be the safest and most effective interventions in those two situations, the first of which is always going to occur because no one stays on any agent forever and the second of which is the clinically vexing one, as our previous discussion.

So I think some formal studies based on what we know about the mechanism of this and other agents should be undertaken to tell people if you're getting someone off, these are ways in which that the chances -- well, the problem is one of powering, but these are ways that seem to work and what the evidence for their working is in terms of reducing the chance of a rapid flare or a loss of benefit. And similarly, if you have someone who's doing badly on the drug, this is what you can do at that time.

I think that's very important missing information that needs formal study as opposed to combination and rotational.

DR. EPPS: Yes. I agree there should be additional studies. Perhaps one drug is better afterwards or perhaps methotrexate shouldn't be used after. I don't know. But I think if it were more formal and patients were followed, that would be helpful. Perhaps overlap or maybe

even combination therapy may be indicated, but I think we need more data before we necessarily get to that point.

DR. SCHMIDT: I agree, but I think that clinical medicine and people in clinical practice are going to determine a lot of this very, very rapidly as we have done with other medications.

DR. RINGEL: I also agree, but the reason I agree that we should do more studies is because clinicians will use it any way and that's a rotten way to collect data. We'll use it. We'll make mistakes. We won't understand that we're having a side effect or that the side effect has happened in a hundred other people. We'll just know it happened in our patient and we won't make anything of it, and because it's going to be used anyway, we really need to have studies so we know what we're doing.

DR. TAN: Yes. I agree with you. There really should be a formal study because this agent or some other systemic agent doesn't have a high response rate. So it's very likely some of the combinations may be highly effective or synergistic. So a formal study will allow you to rigorously evaluate it. That may cure a lot more percent of patients.

MS. KNUDSON: I absolutely agree that more formal studies should be done.

DR. SIEGEL: A number of people around the

table said that it was likely that clinicians would combine this with other anti-psoriatic therapies. I wonder if you could suggest which the therapies are that it's most likely to be combined with, so we know what kind of data would be helpful there.

DR. STERN: I actually think one would need to discuss with the sponsor and perhaps with FDA consultants to really go over a little bit more than we got from the population-based understanding of mechanism prior therapy and what they think would work. I would feel that I really would be winging it more than I usually do to give a response, and I think it would be most useful to have that meeting in a smaller setting, knowing that that's the agenda and really looking at the science of it. I just don't think we can answer that in the next few minutes that we have. But I will let Lynn speak.

DR. DRAKE: Well, I think one of the things that we have to stop to think about is there were some abnormalities in liver functions. Before you start doing combination studies, I think you need to have a little better understanding of what's going on in the liver, and is it directly related to the drug, is it not related to the drug, is it idiosyncratic?

Then before I combine methotrexate with this, I want to have a little better understanding of why those

liver enzymes are mucking around. Before I put them on cyclosporine perhaps or follow up with cyclosporine, what kind of insult has the kidney had, if any?

So my personal opinion is that the safety stuff needs to be clarified a little bit before you can do what Rob suggested and then sit down in a thoughtful manner and try to figure out which rotationals.

Now, if I had to pick a rotational right now, I'd pick a topical. I mean right off the bat, I'd try to move them into the light, which is pretty benign if you don't combine PUVA with it, or if you use the topical steroids, but before you put them on some of the other drugs that have systemic toxicities, I'd want to know more about it.

I still have a level of discomfort about why these lab values are so funky in this stuff, and I think we need to find out a little bit more about it.

DR. SCHMIDT: I think the first thing that I would try with this is hydrea because it lowers the blood count.

DR. DRAKE: Yes.

DR. STERN: I think we've tried at least to respond to the FDA's questions. I know Dr. Plott has been extremely patient and I didn't know if he had any closing comments to make for the record.

DR. PLOTT: I think it's been a good discussion. It would be helpful to ask the agency to put some of these discussions in the context of the clinical studies that were done. A few things like I think the psoriasis adverse events, the sudden withdrawals are things that are characteristic of clinical trials but not characteristic of clinical practice.

A few other things are recommending adequate laboratory monitoring, I think is an appropriate point, and that's about all I can think of offhand.

DR. STERN: Thank you. And if the company had any final comments or in fact questions to the panel. We've asked you a few thousand questions. So do you have any final comments or questions for us?

DR. JOHNSON: If I could say one thing, I think it would be appropriate for us to thank the panel and the FDA for a very fruitful discussion today, but also on behalf of the two companies to thank all of the patients who participated in the studies. Without them, we could not have done this.

Thank you very much.

DR. STERN: And does the FDA have any final questions or comments?

DR. WALTON: I think we have no additional questions, but our comment is to thank all of you for

coming and for really thinking deeply about our knowledge about this product, about our questions and really discussing them thoroughly. The day's discussions are going to be very, very helpful to us in moving forward with this.

Thank you.

DR. STERN: Thank you all very much. The meeting is adjourned.

(Whereupon, at 5:40 p.m., the meeting was adjourned.)