DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

Thursday, May 23, 2002

8:30 a.m.

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Lynn A. Drake, Acting Chair
Karen M. Templeton-Somers, Executive Secretary

MEMBERS

Elizabeth A. Abel, M.D.
Roselyn E. Epps, M.D.
Robert Katz, M.D.
Lloyd E. King, Jr., M.D., Ph.D.
Paula Knudson (Consumer Representative)
Sharon S. Raimer, M.D.
Ming T. Tan, Ph.D.

CONSULTANTS (VOTING)

Warwick L. Morison, M.B., B.S., M.D., M.R.C.P.
Seth R. Stevens, M.D.
J. Richard Taylor, M.D.

GUEST (NON-VOTING)

Robert Swerlick, M.D.

CBER, FDA

Ezio Bonvini, M.D.
Louis Marzella, Ph.D.
Jay Seigel, M.D.
Karen Weiss, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. DRAKE: Hello. My name is Lynn Drake. I am from Harvard Medical School, the Massachusetts General Hospital. I am pleased to be the chair of this meeting.

The first thing I would like to do is open the meeting. This is the Dermatologic and Ophthalmologic Drugs Advisory Committee. First of all, I would like to welcome all the members of the committee. As you know, you had fairly extensive briefing documents. You have had to take a lot of your personal time to review all this and take your time to come here today. We are so appreciative that you have given that volunteer time to help review the product before us today.

I would like to thank the FDA staff, the whole team. The briefing documents were actually very well done. They were concise. They were easy to read and it was clear that effort had been put into it. So I do want to thank the whole FDA staff and team for giving us such a nice group of documents to work from. The preparation was obvious.

I would also like to thank the sponsor for

bringing forward a new drug. You know, we have patients with bad disease and we are always appreciative that you take the time to try to develop a new drug that will help our patients. So we are very grateful to you for bringing forth this new drug.

I also would like to welcome all the guests who are here today. I think public interest in the proceedings in important and significant and so we are grateful. I am particularly pleased that we have some documented participants in the open public hearing. That is delightful to see because we don't always have that and that kind of input just makes us do our job better.

So, having said all that, the first person I would like to introduce is Dr. Karen Templeton-Somers, my Executive Officer for this. She has done a yeoman's amount of work. You can't imagine. Karen, I would like to thank you very much in advance for all the work you have done and all the help you are going to give me today. She keeps me out of trouble. In case you guys don't know what she does, her primary job is to keep me out of trouble from here on out.

The first thing I would like to do so that

everybody knows who everybody is, I would like to go around the table, have the committee members introduce themselves sand your affiliation. I would like to start with Dr. Swerlick.

One of the rules--we have these ridiculous rules here. We have to speak into the mike.

Introduction of Committee

DR. SWERLICK: Robert Swerlick. I am an Associate Professor of Dermatology at Emory University.

DR. TAYLOR: Richard Taylor. I am Professor at the University of Miami and Chief of Dermatology at the Miami V.A. Hospital.

DR. ABEL: Elizabeth Abel. I am Clinical Professor of Dermatology at Stanford in California and in private practice in Mountain View.

MS. KNUDSON: I am Paula Knudson. I am the IRB Coordinator for the University of Texas Health Science Center in Houston.

DR. STEVENS: I am Seth Stevens. I am from University Hospitals of Cleveland. I am Chief of Dermatology at the Cleveland V.A. and at Case Western Reserve University.

DR. KATZ: I am Robert Katz, in the private practice of dermatology in Rockville,

Maryland, Clinical Associate Professor of Dermatology at Georgetown University Hospital.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. MORISON: Lloyd Morison, Professor of Dermatology at Johns Hopkins University.

DR. EPPS: Dr. Roselyn Epps, Chief of the Division of Dermatology, Children's National Medical Center which is affiliated with George Washington University.

DR. KING: Lloyd King, Chief of Dermatology at Vanderbilt University and at the National V.A.

DR. TAN: Ming Tan, Associate Member of Biostatistics, St. Jude Children's Research Hospital.

DR. RAIMER: I'm Sharon Raimer, Chairman of Dermatology at the University of Texas in Galveston.

DR. BONVINI: I am Ezio Bonvini, Division of Monoclonal Antibodies, Center for Biologics.

DR. MARZELLA: I am Louis Marzella, Division of Clinical Trials in the Center for Biologics.

DR. WEISS: Karen Weiss, Division of

Clinical Trials, Center for Biologics.

DR. DRAKE: Terrific. Next, I would like to ask Dr. Somers to please inform us about our conflict of interest statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at the 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.

Dr. Ming Tan has been granted waivers under 18 U.S.C. 208(b)(3) and 595(n)(4) of the FDA Modernization Act for his ownership of stock in a competitor. The stock is valued at between $5,001 to $25,000. Dr. J. Richard Taylor has been granted waivers under 28 U.S.C. 208(b)(1) and 505(n)(4) of the FDA Modernization Act for his employer's contract with a competing firm. The value of the

contract is less than $100,000 per year.

These waivers permit Dr. Tan and Dr. Taylor to participate in the committee's deliberations and vote considering Biologic License Application Submission Tracking Number 125036, Amevive, alefacept, sponsored by Biogen, Incorporated.

A copy of these waive statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

With respect to FDA's invited guest, Dr. Robert Swerlick has a reported interest that we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Swerlick has a financial interest in Immunex and Enbrel.

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 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 firm whose products they may wish to comment upon.

Thank you

DR. DRAKE: Thank you, Dr. Somers.

We have a very packed agenda today. There is a lot of information to be imparted. I will ask the presenters to please stick to your allotted time. If you go over, I will probably have to try to signal you in some capacity because I want to make sure we have plenty of time at the end for the really important stuff.

I would also remind the committee that brevity is wonderful and I will try to remember that same rule, myself. So if we can keep everything as concise as possible, we will move through the agenda and accomplish everything.

With that, let's start. I think the first presenter is Dr. Bonvini from the Division of Monoclonal Antibodies, Office of Therapeutics Research and Review.

Dr. Bonvini, welcome.

BLA 125036, alefacept, Biogen, Incidence.

Introduction

DR. BONVINI: Good morning.

[Slide.]

Madame Chairman, distinguished members of the advisory committee, ladies and gentlemen, good morning.

On behalf of the Center for Biologics, I would like to thank you for your participation in today's discussion of alefacept for the treatment of chronic plaque psoriasis.

[Slide.]

My duty today in the next few minutes is to introduce you to the BLA review committee and introduce the molecular entity under discussion and provide a brief immunological background for the discussion of the clinical data for alefacept. I am Ezio Bonvini and I serve as the Chairman and the product review for alefacept.

The clinical review was the responsibility of Lou Marzella and Electra Papadopoulos. Pharmacologic and toxicology review were performed by Laureen Black and David Green. The statistical review was performed by Chao Wang. Bioresearch monitoring supervision was under the responsibility of Jose Tavarezpagan. Establishing and manufacturing review for alefacept was alefacept was the responsibility of Chiang Syin and Carol

Rehkopt. I would like to acknowledge the excellent regulatory management of Beverly Connor and Lori Tull.

[Slide.]

The molecule for today's discussion is alefacept, also known as Amevive and also identified in a number of publications as LFA3Tip. Alefacept is a fusion protein comprising the human LFA molecule fused with the human IgG-1 FC portion. This molecule dimerizes through the disulfate bond mediated via the IgG portion of the molecule.

As a background to introduce the immunosuppressive mechanism of alefacept, I will briefly review how T-cell activation occurs.

[Slide.]

The activation of T-lymphocyte is a complex mechanism that is centered on the recognition by the clonotypic T-cell receptor of antigen. Now, that doesn't occur in soluble form and the recognition by the T-cell receptor occurs in the context of the major histocompatibility complex of antigen-presenting cells. In addition to the clonal T-PIC receptor, the interaction is assisted by an invariant component, the CD8 or CD4 which interacts with the MHC Class 1 or 2

respectively.

The interaction with the T-cell receptor and the antigen is a low affinity. For a stable association to occur, other molecules intervene and these are called accessory molecules. A critical accessory molecule for the interaction of T-cell with antigen presenter cells is C28 on the surface of T-cells which interact with B7.1 and B7.2.

[Slide.]

But, additional molecules are also involved in mediating this interaction and they include a number additional molecules among which LFA3 is one which interacts with CD2 on the surface of T-cells.

Now the combination of signal via the T-cell receptor and the costimulatory molecules lead to a productive response resulting in lymphokine secretion such as IL2, interferon, and a number of chemotactic lymphokines such as IL8 which lead the T-cell expansion and may be involved in the proinflammatory process underlying the disease under consideration with kerotinocyte proliferation and differentiation.

[Slide.]

Alefacept can interfere with this

mechanism in the context of this complex interaction by either scavenging the physiologic interaction of LFA3 with CD2, by itself engaging CD2

Now, in addition to this competitive mechanism which occur at affinities relatively low and similar to those involving the interaction of endogenous LFA3 with CD2, another mechanism is involved and that is the redirection of a second class of cells, the macrophages and NK cells, via engagement of the Fc receptor through the Fc component of the alefacept fusion protein. This delivers a signal which induces activation of NK cells which delivers a lethal hit.

The susceptibility to NK-mediated lysis of the cells may be different depending on the subtype of cells under consideration.

While the exact mechanism of the susceptibility of T-cells to alefacept-mediated lysis is not fully understood, the T-cell depletion induced by alefacept and its potential for competition with endogenous LFA3-CD2 interaction are central to our discussion of the clinical activity of alefacept and will be touched upon by

Dr. Marzella and Biogen in their review.

[Slide.]

CD2 is expressed prevalently on T-lymphocytes and there is expression on NK cells. B-lymphocytes are largely negative for CD2 expression with only some precursors in the bone marrow being positive.

[Slide.]

The concludes my brief introduction on the immunological background. I need to remind this committee that we are still addressing some outstanding issues pertaining to the manufacturing of alefacept that remain to be resolved. The agency and Biogen are working close together and are trying to address this issue in a timely fashion.

I think I stuck to my time. This concludes my presentation. I could take questions or just give the podium to Biogen.

DR. DRAKE: I think you did a great job. Do any of the committee members have a pertinent question about the presentation? I'm sure we will have some later. Thank you, sir.

DR. BONVINI: Okay.

DR. DRAKE: I think we have a latecomer to

the meeting, but we are delighted. Dr. Seigel, I presume?

DR. SEIGEL: Yes.

DR. DRAKE: Welcome. We are delighted to have you here.

DR. SEIGEL: Thank you. Pleased to be here.

DR. DRAKE: I had just complimented you and your team for a very nice presentation of the documents. We are very grateful when it is so well done.

DR. SEIGEL: Thank you very much.

DR. DRAKE: Moving forward, now it is time for the sponsor which is Biogen for their presentations. I believe the overview will be given by Dr. Adelman.

Sponsor Presentation, Biogen, Inc.

Introduction

DR. ADELMAN: Thank you, Madame Chairwoman. Good morning, members of the panel, colleagues from CBER and members of the audience.

[Slide.]

My name is Burt Adelman. I am the Executive Vice President of Research and Development at Biogen. Much of our research

efforts at Biogen are focused on understanding autoimmunity and developing therapeutic strategies to treat autoimmune diseases. Today, as a result of these efforts, we are pleased to be here to discuss alefacept, a new agent that we have developed for the treatment of chronic plaque psoriasis.

[Slide.]

Our presentation will focus on data that we believe supports the following indication. Alefacept is indicated for the treatment of patients with chronic plaque psoriasis who are candidates for systemic or phototherapy. Alefacept is a parenteral agent and we recommend a dosing regimen as listed here, once per week dosing for 12 weeks.

The drug can be administered either as a 7.5 milligram intravenous bolus injection once a week or a 15 milligram intramuscular injection once a week. Repeat courses can be given after a 12-week rest period.

[Slide.]

Our agenda this morning is listed here. I will provide a brief overview of the product. Dr. Akshay Vaishnaw, Medical Director at Biogen, will

talk about the clinical efficacy of the alefacept and describe the pharmacodynamics. Dr. Gloria Vigliani, Vice President of Medical Research at Biogen will speak about the clinical safety profile. Finally, we have invited Dr. Mark Lebwohl, a distinguished expert in the field of psoriasis to provide a perspective from the clinical view on the risk-benefit profile of alefacept.

[Slide.]

In addition to Dr. Lebwohl, we are fortunate to have with us a number of other distinguished consultants. These include Dr. Richard Cooper, a hematologist, Professor of Medicine at the Medical College of Wisconsin; Dr. David Margolis, Associate Professor of Dermatology and Epidemiology at the University of Pennsylvania and Dr. James Krueger, Associate Professor and physician at the Rockefeller University. Dr. Krueger heads the Laboratory of Investigative Dermatology at that Institution.

Although they will not be making formal presentations, they are here to help with the discussion and answer any questions that may arise.

[Slide.]

Now, to begin my review. Chronic plaque psoriasis is recognized to be a T-cell mediated disease. Men and women are affected equally. Although it is recognized that there is a strong genetic component to this disorder, the exact genes that drive the disorder have yet to be identified.

In appearance, the skin lesion of psoriasis is a circumscribed red raised plaque. These plaques are often itchy and scaly and can crack and bleed. Psoriasis can also be associated with a number of systemic manifestations, the most common of which is psoriatic arthritis. Individuals with moderate to severe psoriasis typically have lesions covering 10 percent or more of their body-surface area. As you will have seen in the briefing document that we distributed, a number of the patients in our studies actually had skin involvement of up to 98 percent of their body-surface area. Psoriasis is a life-long disease and, as yet, there is no cure.

[Slide.]

Here is a picture of the disease that we are speaking about. This is a patient from one of our Phase 3 studies, a gentleman with moderate to severe chronic plaque psoriasis. It is not hard to

understand that this disease, in addition to the clinical manifestations, has a debilitating impact on a patient's life.

John Updike, in his essay, At War with My Skin, describes poignantly his own personal experience with psoriasis. "They glance at me and glance away pained. My hands and my face mark me. The name of the disease, spiritually speaking, is Humiliation."

[Slide.]

This statement powerfully captures the psychosocial burden that many individuals with psoriasis suffer. In fact, this has been studied and, to some degree, quantified. Quality of life is identified as being severely impacted in patients with moderate to severe psoriasis. The impact is similar to that of other serious diseases such as chronic congestive heart failure and advanced diabetes mellitus.

Understandably, these effects correlate with the increased risk of substance abuse, depression and suicidal ideation commonly seen in the psoriasis population. Common comorbidities of psoriasis include obesity, heart disease, diabetes and hepatitis.

For all these reasons, patients and their physicians are often searching for new therapies and patients with advanced psoriasis often seek out and are commonly treated with aggressive therapies.

[Slide.]

Current therapies to treat chronic plaque psoriasis are listed here, systemic therapies. There are two types. In the upper part of the slide, I have indicated the disease-suppressive therapies. In the lower part are the remittive therapies.

The suppressive therapies, methotrexate, retinoids and cyclosporine effectively treat the disease as long as the patient takes them. When therapies are withdrawn, there is usually reasonably rapid return of disease, hence the label suppressive. Remittive therapies such as PUVA an UVB, light-based therapies, can provide disease-free periods. However, to obtain these results, patients must undergo frequent and repeat treatment cycles.

Each of these important therapies is associated with one or more toxicity that is significant, commonly observed and often limits it use.

[Slide.]

For example, methotrexate can cause hepatic fibrosis and patients who receive over a gram and a half of methotrexate often are required to have a liver biopsy to determine whether they can receive additional therapy. Cyclosporine is commonly associated with nephrosis and, therefore, patients cannot take cyclosporine continuously for more than a year.

Phototherapy with PUVA has been documented to increase patient risk for squamous-cell carcinoma and melanoma. So, again, significant limitations for therapy.

So, while these therapies provide meaningful efficacy, their use also imposes significant risk. In an effort to balance toxicity and maintain reasonable disease control, dermatologists have evolved a strategy of disease management based on rotating the available therapies. Clearly, new therapies, particularly remittive agents that can induce a long duration of effect will favorably impact this strategy of rotational therapy.

It is to address this significant unmet need that we have developed alefacept.

[Slide.]

To understand the rationale behind the development of alefacept as a new immunomodulator, I would like to briefly review the pathobiology of psoriasis. As indicated a few slides ago, psoriasis is clearly recognized to be a T-cell-mediated disorder. In particular, memory T-cell subsets play a critical role in a pathogenesis of the psoriatic plaque.

In this section from a skin biopsy of a patient with psoriasis, memory T-cells are seen infiltrating the skin underlying the proliferative response. These active cells are derived from CD4 and CD8 cells and are identified by a characteristic cell-surface marker called CD45RO-positive. It can be stained for and these cells can, therefore, be uniquely identified.

Once in the skin, again as we see here, these activated CD45RO-positive cells release a spectrum of inflammatory mediators that stimulate kerotinocyte proliferation and blood-vessel growth resulting in the characteristic psoriatic plaque.

[Slide.]

The cells that I have described can be identified in the blood and in the lymph organs.

This cartoon indicates the composition of leukocytes in the blood. You can see that memory CD45RO-positive cells are constituent of the T-cell CD4 and CD8 population within the blood and they can be distinguished from naive cells by this characteristic marker.

Our data suggest that alefacept selectively targets CD4 and CD8 memory cells and it does this through its activity against the CD2 ligand on memory cells.

[Slide.]

Dr. Bonvini has taken you through this and with somewhat more elegant slides. Perhaps he will lend them to me in the future. But I will take you through this mechanism again.

A naive T-cell that has never previously seen antigen will interact with antigen-presenting cells by way of the MHC and T-cell receptor. But, as already mentioned, this interaction is inadequate to result in T-cell activation and, importantly, costimulatory pathways mediated through coupling of LFA-3 and CD2 and B7 and CD28 are also necessary. In fact, this cartoon is, itself, a simplification and there are other additionally important costimulatory pathways.

As a result of these events, the naive T-cell becomes activated. During the activation process, a number of characteristic changes occur. The cells proliferate so, in fact, there would be more cells here than just the one and a number of changes occur on the surface. In particular, there is increased expression of CD2 on the surface of these CD45RO-positive cells.

This conversion from the CD2 low state to the CD2 high state is what we think imparts the selectivity of alefacept to the CD45RO-positive memory cell.

Just, also, by way of historical background, LFA3 was actually cloned at Biogen and, very early on, we understood the significance of the LFA3-CD2 interaction and that is why we have chosen this particular pathway to develop a drug that interferes with this process.

[Slide.]

Here, again, is a picture of alefacept. As you can see, it includes the extracellular domain of human LFA3 fused to a portion of human IgG1 and is, therefore, called a fusion protein. It is expressed as a dimer which is held together by cysteine bonds and, although it looks like an

immunoglobulin, it is not an immunoglobulin. It is a fusion protein.

Now, the sequence is entirely human and that is why there is very little antigenicity associated with the use of this.

[Slide.]

I would like to review again alefacept actions as are illustrated in this slide. Alefacept can block LFA3 CD2 interactions thereby inhibiting reactivation of memory T-cells. As indicated here, alefacept would bind to CD2 and stearically interfere with the docking to an antigen-presenting cell.

Again, as Dr. Bonvini already indicated, another effect is also mediated by alefacept. Alefacept combined via the FC receptor on certain cells such as natural killer cells and induce a pro-apoptotic response. This is mediated through the release of a protein called granzyme which initiates apoptosis in the memory T-cell resulting in its loss.

This is a generalized model. We believe that this model applies at the doses that are recommended for use to treat psoriasis but there may be specifics about how this mechanism works in

the skin, in the blood and in lymph tissue and we are fortunate to have Dr. Krueger here with us today who has studied this extensively and, perhaps, during the question period, he can comment further on the specifics of this effect.

[Slide.]

This mechanism of action was tested in a blinded placebo-controlled dose-ranging Phase-II study in approximately 230 patients with moderate to severe psoriasis. I have illustrated the results here, in particular looking at the effects on CD4-positive memory cells. So these would be CD45RO-positive cells that are also CD4 positive and CD4 positive naive T-cell, unactivated T-cells, that would not express CD45RO.

What you can see--this was a dose-response study. Here is the twelve-week dosing period and this is a twelve-week follow-up period. This is the placebo dose and here are increasing doses of alefacept. You can see that, with increasing doses, there is increased reduction in the number of CD4-positive memory T-cells and the cell counts start to recover after discontinuation.

In contrast, there is minimal effect, if any, on the naive T-cells during the same dosing

period. It was these pharmacodynamic effects coupled with the clinical effects that we observed in this study that led to the development of the clinical program for alefacept in chronic plaque psoriasis. We are here to discuss those results today.

[Slide.]

I would like to provide some additional background on the overall program. We have conducted an extensive toxicology program to support alefacept development. In fact, we have completed 35 toxicology studies in nonhuman primates. We are fortunate because a nonhuman primate responds somewhat similarly to humans in that we can observe impacts on T-cell numbers and we can look at the effect that this may have in the lymph nodes and we can watch recovery.

For testing purposes, we have used regimens up to 20 milligrams per kilogram IV weekly for one year. This dosing regimen, obviously, greatly exaggerates the recommended dosing regimen in people, both in terms of magnitude of drug delivered and length of continuous exposure.

[Slide.]

Here I have summarized the results of the

toxicology program for you. Alefacept was well-tolerated in these animals. We observed reversible decreases in lymphocyte counts, both in blood and lymphoid tissues. No opportunistic infections were observed in any treated animal and no reproductive toxicity was observed.

I would like to comment on one observation that was outlined for you in the briefing document. In a single cyno monkey receiving 20 milligrams per kilogram of alefacept weekly, we diagnosed the occurrence of a B-cell lymphoma. This monkey was part of a long-term treatment study and, as I have mentioned, received a very high dose continuously for 28 weeks.

In fact, this dose is the equivalent of 622 clinical courses. So we made this observation in the setting of a highly exaggerated dosing schedule. This was the only observation of lymphoma in over 200 animals treated across various preclinical studies.

[Slide.]

This next slide briefly outlines the clinical program for alefacept which you will be hearing in much more detail later this morning. We have conducted 18 clinical studies and treated

1,357 patients with chronic plaque psoriasis and 240 healthy volunteers.

The core of our presentation focuses on three randomized double-blind placebo-controlled studies in patients with chronic plaque psoriasis. One is a Phase 2 study and the other two Phase 3 studies. These studies will be discussed in detail by Dr. Vaishnaw.

We, at Biogen, are committed to understanding both the short and long-term safety issues associated with the introduction of alefacept as we would be with any new drug being introduced into the community. We believe that active monitoring of patients on therapy for extended periods of time, even after a product is approved, should be a key component of an integrated, long-term safety and development program.

For these reasons, most of the patients coming out of our randomized clinical trials have been given the opportunity to enter into a comprehensive extended safety dosing study. In fact, at this point in time, over 800 patients are currently in extended safety dosing studies. Already, some of these individuals have received as

many as five treatment courses over a three-year period of time and it is our intention to extend this program indefinitely and probably to expand it.

[Slide.]

Because alefacept targets memory T-cells, we have already begun to study its effects in other autoimmune disorders with a T-cell-mediated etiology. Currently, in addition to psoriasis, we are studying psoriatic arthritis, rheumatoid arthritis and sclera derma and, in fact, we summarized for you, in your briefing document, the results of a small study in psoriatic arthritis.

[Slide.]

Throughout the development history of this program, we have had a close collaboration with our colleagues at CBER. We are grateful to them for their interest and guidance in all aspects of the preclinical, clinical and manufacturing programs.

The regulatory history of alefacept is outlined here. In August of 1996, we had a pre-IND meeting with the agency and, shortly thereafter, launched our program in the United States. In 1999, and end-of-Phase-II meeting was held to discuss our positive findings. After agreement

with the agency on the design of the Phase 3 program, we moved forward to begin the studies that we will be discussing today.

Now, importantly, the safety database in this document is consistent with ICH guidelines. In July of last year, we met again with CBER to discuss our Phase 3 results and plan for filing an electronic biologics license application. In August of 2001, we filed the application which we are happy to be here to discuss with you today. Now, in March of 2002, we provided the agency with an extensive safety update to this document.

Now it is my pleasure to introduce Dr. Vaishnaw who will take you through clinical details of our program. Thank you for your attention.

Clinical Experience

DR. VAISHNAW: Thank you.

[Slide.]

Madame Chairperson, members of the panel, ladies and gentlemen, good morning. I am Akshay Vaishnaw. I am a member of the medical team at Biogen. I have been involved with the development of alefacept.

I shall be describing two components of the clinical experience to you today, namely the

efficacy and pharmacodynamic aspects of the program.

[Slide.]

I have divided the efficacy part of the presentation beginning with a brief overview of the Phase 2 study and following with a detailed analysis of the Phase 3 studies both the IM and IM protocols. I will then move to a description of the quality-of-life improvement seen after alefacept therapy and close with a discussion of the efficacy in some important subpopulations of patients.

[Slide.]

There are three randomized placebo-controlled trials that are at the core of the program; a Phase 2 IV study and two Phase 3 studies, one by the IM route and one by the IV route.

You can see that in the Phase 2 study, we dosed patients on a body-weight basis. Here you can see that is indicated as dosing in milligram per kilogram. Other studies during Phase 2 indicated that body weight did not significantly influence the pharmacokinetics of alefacept and, therefore, in Phase 3, we transitioned to the more

convenient fixed-dose regimens as indicated here.

As you look to the right of this slide, you can see that a substantial number of patients, in fact over 1300 patients, were enrolled in these three studies making them some of the largest chronic-plaque-psoriasis studies ever.

[Slide.]

The findings from the Phase 2 study were published by Drs. Charles Ellis and Gerry Krueger in an article in The New England Journal of Medicine last year and their major findings were summarized as follows. They detected that alefacept was associated with clinically meaningful efficacy and it was superior to placebo. They determined that it had a significant duration of benefit.

Patients that had cleared their disease had a median time to retreatment of ten months. With respect to T-cells, given the mechanism of action, they clearly illustrated that alefacept was selective for reductions in memory T-cells with sparing of naive T-cells. Importantly, these changes correlated with efficacy outcomes. This validated the therapeutic rationale in the approach to Phase 3. Finally, the Ellis and Krueger study

allowed us to pick the optimum dose group for Phase 3.

With that, I want to turn to the Phase 3 studies.

[Slide.]

At baseline in the Phase 3 studies, all the important background demographic and disease-severity factors were well balanced. I want to consider some factors related to disease status at baseline.

Here you see data for the two Phase 3 studies, the IM and IV protocols. The median duration of disease at baseline ranged between eighteen and nineteen years. In other words, these patients had established chronic plaque psoriasis.

If you look at the next three rows, the body-surface area involvement, the PASI score and the physician global, each reveals that patients had moderate to severe chronic plaque psoriasis at baseline.

[Slide.]

Let me illustrate that by considering the BSA score. The median BSA at baseline ranged between 21 and 22 percent in these studies. Now, if we imagined that one palm size is about 1

percent of our body-surface area, then 22 percent average involvement is extensive chronic plaque psoriasis and a significant burden of disease to these patients at baseline.

That conclusion is supported by the median PASI score in the mid-15s and the physician global assessment where over 80 percent of patients had disease severity ranging between moderate to severe.

[Slide.]

I have already mentioned the PASI. PASI will be central to a lot of our discussions regarding efficacy today. PASI is, in fact, an acronym of the Psoriasis Area and Severity Index. It is a widely used tool in psoriasis clinical trials in order to quantify and follow disease activity over time. It is a composite measure and involves measurement of erythema, induration, desquamation and the extent of body-surface area involved.

Those four parameters are evaluated over four parts of the anatomy; the head, the trunk, the upper limbs and the lower limbs. Those data are put into a formula resulting in a composite score which ranges from 0 to 72. 0 is clear or healthy

skin. 72 is disease of maximum severity.

A score between the range of 10 and 30 typically summarizes patients with moderate to severe chronic plaque psoriasis.

[Slide.]

Three endpoints will be discussed with respect to the clinical trials we are reviewing today. These are PASI 75--that is a 75 percent or greater reduction from baseline disease severity with respect to the PASI tool, a very stringent endpoint. The next endpoint is PASI 50, a 50 percent or greater reduction from baseline disease severity. Finally, the third stringent endpoint is the physician global assessment of almost clear or clear.

These two endpoints were read out both two weeks after the last dose in the studies and also in what we term the overall response rate. I want to illustrate what I mean by that on the following diagram.

[Slide.]

Here is a typical randomized placebo study comparing placebo to alefacept. On the left-hand part of the diagram, you can see the dosing interval. Patients are receiving injections for

the first twelve weeks. On the right-hand side, you can see they are followed for another twelve weeks. That 12-plus-12 interval we term a course of alefacept therapy.

Now, the primary efficacy endpoint was conducted as a landmark analysis two weeks after last dose at this single time point. Given that in Phase 2 and in other studies we had determined that alefacept patients often reach maximal efficacy at other times often late in the follow-up interval here, we also determined the overall response rate for patients that achieved PASI 75 and the other endpoints at any time during the course of therapy.

[Slide.]

Before we actually consider the efficacy data, I want to, with the use of a few pictures, consider what a PASI 50 and PASI 75 response is like. It can be difficult to conceptualize them in the abstract.

Here is a patient on the left who, at baseline, has had extensive chronic plaque psoriasis effect from the midline, the area above the buttocks and the backs of the arms. This is a patient with a score of 18.7 by the PASI 2 and baseline. After treatment, the score is 5.7. This

patient has an almost 70 percent reduction in PASI.

This patient would not qualify for the primary-efficacy endpoint of PASI 75 but would qualify for PASI 50. She doesn't qualify for PASI 50. She doesn't qualify for PASI 75 because she has never attained 75 or greater.

[Slide.]

Contrasting that to the PASI 75 response, on the left you see a young person with extensive disease again affecting the torso and the lower limbs. His score is 34.3 at baseline. After treatment, his score is 4.2. The percentage positive reduction is 88. This gentleman would qualify as a PASI 75 responder.

[Slide.]

With that background, I want to review the two major studies, first the Phase 3 IM study.

[Slide.]

In the Phase 3 IM study, patients were screened and randomized to one of three arms, placebo or alefacept 10 milligrams or alefacept 15 milligrams. They received the injections once a week IM for 12 weeks on the left-hand side of the diagram and then there was a 12-week follow-up interval. The primary efficacy endpoint was read

out as a landmark analysis two weeks after last dose. The primary endpoint was PASI 75.

Note that the endpoint was read out without the use of disqualifying medications; by this, I mean major, high-potency topical steroids or the major systemic antipsoriatic agents, and the range of UV therapies that are commonly used.

If patients used any of those disqualifying medications prior to the primary efficacy endpoint, they were classified as a treatment failure. If patients did not show up for the primary efficacy-endpoint visit, they were, again, classified as a treatment failure. This is a relatively conservative approach when documenting efficacy data.

The rules regarding disqualifying medications also apply to all the other efficacy data we are going to review today.

[Slide.]

In the Phase 3 IM study, PASI 75 score two weeks after last dose was 21 percent in the 15 milligram group and 5 percent in the placebo group. This difference was highly statistically significant and the Phase 3 IM study, therefore, met the primary efficacy endpoint.

In the middle you can see that, in the 10-milligram group, 12 percent of patients attained the endpoint contributing to this nice dose response between placebo and 15 milligrams.

The findings from this PASI 75 tool was strongly supported by an independent measurement, namely the physician global of almost clear or clear.

[Slide.]

Here you can see on the right that 14 percent of patients in the 15-milligram group cleared their disease versus 5 percent in the placebo group. The difference was highly statistically significant.

[Slide.]

Finally, the third of the endpoints also supported the conclusion that alefacept was superior to placebo with 42 percent of patients in the 15-milligram group achieving the endpoint, 18 percent in placebo. So, over a series of endpoints, all stringent, we have demonstrated that alefacept monotherapy was significantly superior to placebo.

[Slide.]

I have just conveyed some of the landmark

analyses two weeks after last dose. I want to contrast the findings from those to those for the overall response rate where patients were achieving the endpoint at times other than just two weeks after last dose.

On the right, you can see patients who hit PASI 75 at any time during a course of therapy as shown with 33 percent in the yellow in the 15-milligram group achieving PASI 75. This is significantly greater than the 21 percent by the landmark analysis.

You see increments for all three treatment groups on the right compared to the left, but the data on the right conveyed that these patients in the alefacept group had more sustained responses than those in the placebo group here, and we therefore believe that the overall response-rate data for each of the endpoints we will be discussing today reflect the true clinical attributes of alefacept and what patients can expect to experience in terms of the course of therapy.

[Slide.]

I am going to turn now to the Phase 3 IV study. Patients were screened here and randomized

to one of three arms, Cohort 1, Cohort 2 or Cohort 3. All three cohorts received two courses of therapy, as indicated. Each course was 24 weeks long.

Cohort 1 received alefacept in the first course followed by alefacept in the second. Cohort 2 received alefacept followed by placebo. Cohort 3 received placebo followed by alefacept. The primary efficacy endpoint, as for the IM study, was PASI 75 two weeks after last dose, again without the use of disqualifying medications.

The advantage of this type of study, apart from the primary efficacy endpoint for the placebo-controlled component of the program here was we could also ask the question, did repeated courses of alefacept result in evidence for incremental efficacy by examining outcomes in Course 2 for alefacept with the outcomes in Course 1.

By examining outcomes for Cohort 2 who received a single course of treatment, when they are off therapy for this 36-week period, we could determine how sustained was the efficacy after 12 injections. So, with that, let me actually turn now to the data.

[Slide.]

Here we have summarized the three endpoints we have spoken of, the outcomes two weeks after last dose in the first course. Let's focus first on the far left, PASI 75, which is the primary efficacy endpoint for this study. 14 percent of patients in the alefacept group achieved the endpoint, 4 percent in the placebo group. This difference was highly statistically significant. So, again, for the Phase 3 IV study, we met the primary efficacy endpoint as prespecified.

The data from the other two endpoints again support the conclusions from the primary efficacy endpoint, the physician global, alefacept 11 percent, placebo 4 and, for PASI 50, 38 percent of patients achieved the endpoint versus 10 percent in the placebo.

Now, examining outcomes for Cohort 1 in the second course, we detected evidence of incremental efficacy as shown here in yellow. You see that, for each of the three endpoints I have just described, the response rates increased in the second course. Considering the PASI 75, the response rate when from 14 to 23 percent, a very significant increment, similarly, for physician global and PASI 50.

[Slide.]

Now, to contrast those landmark analyses two weeks after last dose in each course to the overall response rate where patients responded at other times during the course of therapy.

Concentrating first on PASI 75, far left, you can see in the alefacept subgroup 28 percent of patients responded at some point during the course of the first course of therapy. This is a doubling of the primary efficacy-endpoint data, 14 percent. The difference here is statistically highly significantly superior to placebo.

The evidence of an incremental rise in these overall response rates is also seen for the physician global and PASI 50 with over half the patients achieving PASI 50 in the first course of therapy.

If we look at the overall response rates in the second course, we see evidence of incremental efficacy, 37 percent of PASI 50, 30 percent for patients clearing their disease and 64 percent--that is, almost two-thirds of patients--achieved PASI 50 during the second course of therapy.

[Slide.]

Now, an important area of ummet need and an important attribute of potentially new therapies or agents that could put the disease into remission; we were interested to calculate whether alefacept had disease-remittive properties and, to do that, we analyzed the data from Cohort 2 who received the twelve weeks of treatment and 36 weeks of follow up.

We calculated the duration of remission for those patients that had achieved the most stringent endpoint, PASI 75, during Course 1. The duration of remission was defined as the time spent in response at PASI 50 or better.

The median duration of remission, as defined, was seven months. This appears to be significant and to suggest that alefacept is a disease-remittive type of agent and the first systemic immunotherapy to have this type of property. The data also consolidates the findings from the Ellis and Krueger paper in The New England Journal of Medicine where they also demonstrated efficacy duration suggestive of disease-remittive properties.

[Slide.]

Here is a graphical representation of this

same data. We are looking at the PASI-50-or-better response in those that achieved PASI 75, Cohort 2 in the Phase 3 IV study. The Kaplan-Meier curve tracks the duration of time patients are in a response of PASI 50 or better.

You can see 50 percent of patients are at this level of response for 211 days or more. So, again PASI 50 or better is maintained for a period of seven months for the median number of patients.

[Slide.]

The other important area of unmet need for chronic-plaque-psoriasis patients is the tremendous quality-of-life deficit these patients suffer. We were obliged to understand whether alefacept treatment improved the quality of life.

[Slide.]

To do this, we used the tool termed the DLQI, or the Dermatology Life Quality Index first described by Finlay and Kahn in 1994. It has been used fairly widely in dermatologic studies including psoriasis studies.

On the left, you see the data for the changes in DLQI for placebo versus 7.5 milligrams IV for the Phase 3 IV study. On the right, you are seeing the corresponding data for the Phase 3 IM

study.

Looking on the left at the Phase 3 IV data, there is a reduction in the DLQI score for those in the placebo group, 11 to 9.9. I should remind you that the reduction in score is an improvement in quality of life. In the alefacept, 7.5 milligram group, there is a significant reduction from 11 to 7.6.

The conclusion that alefacept is associated with statistically significant reductions in DLQI scores was also seen in the Phase 3 IM study as indicated on the right here.

[Slide.]

These types of data don't fully convey the potential quality-of-life improvements patients can experience. To begin to do that, the next two slides address the issue of to what extent are patients really improving.

Firstly, to what extent did patients improve if they achieved PASI 75, if they achieved PASI 50 or they achieved physician global. These data are from the responders in the Phase 3 IV study. It is a pooled analysis irrespective of whether the patient was in the placebo group or in the alefacept groups. Looking at the PASI 75

response, you can see the score transition is from 11 pretreatment to 2.4 if you achieve PASI 75 with alefacept. That is a significant reduction.

Similarly, if you go to the right, you can look at the physician global. The transition is from 10.4 to 2.4, again a very extensive reduction. Those data are not surprising because these are very stringent endpoints but we were surprised to see that, for PASI 50, the score went from 11.6 to 4.2, another very significant improvement in the quality of life.

This data begins to give insight into the importance of PASI 50 as an important endpoint for these patients to achieve with this burden of disease.

[Slide.]

Finally, to give the ultimate granularity of what quality-of-life improvement means to patients, here are data from the actual subcomponents of the DLQI score for 15 milligram group in the Phase 3 IM study. There are similar data for the other treatment groups. What I want to discuss is the extent to which patients that reported being at the severe end of the scale for each of these questions changed from baseline to

two weeks after last dose.

So it is a five-point scale and at baseline patients are meant to fill out a questionnaire saying how much embarrassment did they suffer. The most extreme end of the scale is very much or a lot. The proportion who answered at that level at baseline was 64 percent consistent with the disease burden they have.

After twelve weeks of treatment, 27 percent of patients in the 15-milligram group experienced the same level of embarrassment. Their impact on daily activities transitioned from 21 percent having very great difficulties to 7 percent and as you go on down the table.

This is across the treatment groups. If you look at the same data for patients who responded to the various endpoints, you see even further improvements or greater improvements in these important quality-of-life domains.

[Slide.]

Finally, I would like to close the issue with a discussion of outcomes in some important subpopulations.

[Slide.]

First, the outcomes as a function of

disease severity at baseline. There appear to be a lot of ways to quantify disease severity. We have chosen one standard approach here. Severe disease is body-surface area greater than 30 percent at baseline. Less severe disease is body-surface area involved in less than 30.

On the right, you can see the proportions of patients with a BSA greater than 30 who achieve the primary efficacy endpoint, 13.8 in the alefacept group in Phase 3 IV study versus 5.6 in the placebo group. The difference is significant.

The same magnitude is seen in the BSA less-than-30 group, 16.2 in the alefacept group versus 4.1. We have concluded that alefacept efficacy is not significantly influenced by baseline disease severity and patients with a broad range of disease severity can be helped by the drug.

[Slide.]

Now, a similar pooled analysis of all Phase 3 patients so that we have very big numbers here was done for patients based upon their prior response status. About 80 percent of patients in the Phase 3 studies reported having one of the major systemic antipsoriatic agents or UV therapy

prior to entering into our studies.

Those patients were classified based upon their responses as having no change or worsening on the previous therapies, improving on previous therapy or no prior treatment; i.e., naive to the previous therapies.

Then, for each of those groups, we assessed the primary efficacy endpoint. For those that had not changed on the previous treatments or worsened, 20.2 percent responded to alefacept. 3.1 responded in the placebo group. This difference was highly statistically significant. The same kind of data is seen for those that also improved on previous treatments and for those that were naive to previous treatments.

So this analysis supports the conclusion that alefacept is efficacious in a broad range of patients irrespective of their response to previous agents.

[Slide.]

To summarize the efficacy part of the presentation, we have concluded that alefacept is effective in reducing psoriasis disease activity. We have done this by three independent randomized placebo-controlled studies. These encompass both

the IV and the IM routes. The data, as we have discussed, are consistent and robust across all endpoints and in important subpopulations of patients.

In the Phase 3 IV study, we demonstrated a greater evidence of response with the second course of therapy--in other words, incremental efficacy--and we demonstrated extended durations of remission of seven months in patients that achieved PASI 75 during the Phase 3 IV study.

Finally, and most importantly, perhaps, alefacept therapy has been shown to improve the quality of life of patients in the course of both our Phase 2 and Phase 3 studies.

[Slide.]

I would now like to move to the pharmacodynamics. Both Dr. Bonvini and Dr. Adelman have elegantly described the mechanism of action to you. I now want to review the range of alefacept-mediated lymphocyte effects that we documented in Phases II and III.

To do that, I will focus specifically on the Phase 3 IV study, the two-course study. We have similar data from the Phase 2 study and also the Phase 3 IM study. These were summarized in

your briefing documents.

[Slide.]

I will consider both the mean counts over time to convey the range of qualitative changes that we can expect to see and also convey the individual patient experience because there are data of clinical relevance that we should discuss.

Finally, I will close with a discussion of the potential implications of the types of changes we have seen with a specific question as to what are the role of memory T-cells given that they are targeted selectively by the agent. After doing that, I want to consider what data do we have that addresses does Biogen have evidence for integrity of immune function in alefacept-treated patients.

[Slide.]

Here you see a diagram which is just a variant of one that Dr. Adelman showed you earlier. These are the major lymphocyte subpopulations in our peripheral blood and lymphoid tissues. They are dominated by two species, the CD4 and CD8 T-cell. The CD4 T-cells are of two types. They are either naive or they are memory.

CD8 T-cells, again, are of the same two types, CD8 naive or CD8 memory. You will see data

demonstrating that alefacept selectively targets CD4 and CD8 memory T-cells. From this diagram, you can see that a reduction in CD4 or CD8 memory T-cells would result in a reduction in the total CD4 T-cell count or a reduction of the total CD8 T-cell count.

Those reductions, in turn, would summate to result in a reduction of the total lymphocyte count which can be easily assayed by the CBC.

[Slide.]

With that background, let me begin to demonstrate the range of features. This graph summarizes what is at the core of the program, the selective effect of alefacept against memory T-cells. On the left, you see the effect on CD4 memory T-cells, on the right, the effect on naive T-cells. It is immediately apparent that, in the memory compartment, there is no significant effect in the placebo group but, in the Phase 3 IV study, the dosing period was associated with a reduction in counts during the dosing interval.

Contrasting that to the findings on the right, you see no significant changes in the naive CD4 T-cells in either the placebo or the alefacept-treated patients. We have identical data for the

CD8 memory and naive T-cells.

[Slide.]

Taking the CD4 memory T-cells a step further, changes in this compartment would result in a change in CD4 memory T-cells as a whole. Those changes are illustrated here. You can see, on the dotted line, no significant changes in the placebo group during dose and a significant reduction in alefacept during the dosing interval with an increasing count following withdrawal of treatment.

At all timepoints, just as we saw for total lymphocyte counts, the mean, and I emphasize the mean, CD4 T-cell count, remains above the low limit of normal.

[Slide.]

Finally, the total lymphocyte count; you can see, again, in placebo, no significant changes. In alefacept, significant reduction during dosing and increasing counts upon withdrawal of therapy. Again, the mean counts remain above the low limit of normal.

So that is one course of therapy. Cohort 1 in the Phase 3 IV study had two courses of therapy.

[Slide.]

The mean CD4 T-cell changes for that cohort are illustrated on this graph. On the left, you see the Course 1 data. On the right, you see the Course 2 data for the same patients. There are three features in common that I want to go through here. Number one, the rate of change during the dosing interval is identical between Courses 1 and 2.

Number 2, the nadir reach for mean counts is identical between Courses 1 and 2. Finally, the rate of increase following withdrawal of therapy is also identical between Courses 1 and 2. Note that while patients are on alefacept therapy when drug is withdrawn, they haven't, as yet, reached baseline. At all timepoints, patients maintain mean counts above the low limit of normal.

[Slide.]

Contrasting those ranges of features considering the entire treatment groups and starting to look at individual patients, we can see the range of effects. To do the most conservative analysis, what we illustrate here are the patients that experienced total lymphocyte in the first row, CD4 in the second row and CD8 in the third row.

Counts below the lower limit of normal at any time point during the course of the Phase 3 IV studies either in Course 1 or in Course 2. These are the same patients dosed in both intervals.

This is a conservative approach because we count patients, even if they went below normal just on one occasion and came back. Given that most individual's counts are very volatile, this is probably an overestimate of the data. But it is important we go through these carefully.

For total lymphocyte counts, the proportions that went below normal in the first course were 18 percent in the first course and 17 percent in the second. The CD4 T-cell count, the proportions below normal, first course 44, second course 44. For CD8 T-cell count, 51 percent in the first course and a suggestion of incremental events with 56 percent in the second course.

[Slide.]

If patients go below normal, then how did they achieve counts within the normal range. I have illustrated that here by looking at patients who achieve counts to within the normal range after twelve injections of IV therapy. These are data from the Cohort 2 in the Phase 3 IV study whom, you

will recall, have twelve weeks of treatment and then we followed for a 36-week period off drug. That 36-week interval is the time course on this X-axis.

The Y-axis illustrates the proportions who achieve counts within the normal range. Immediately after the twelve injections, you can see 63 percent of patients have counts within the normal range. As we follow patients out, you can see that, by Day 180, 90 percent of patients have achieved a count within the normal range.

Finally, as we look at the last time point, it appears that there are patients who are missing while these are patients, 16 patients, who, almost in all cases, were lost to follow up. Some of these patients at the last point of observation had counts between 300 to 400, but they disappeared at any time during this interval and, for purposes of summary, we just leave them missing here.

[Slide.]

The range of alefacept effects, I have just described, are based upon careful monitoring. In the Phase 3 studies, dosing was only initiated in those with CD4 T-cell counts in the normal range. Dose admission was carried out with

substitution of placebo for those patients that had a CD4 T-cell count under 250 recalling that the low limit of normal is 404 cells per microliter.

Finally, moving forwards, despite the fact that we have not found any evidence of immunodeficiency associated with the lower T-cell counts, we propose a conservative approach, CD4 T-cell monitoring every two weeks during therapy.

[Slide.]

Having gone through the phenomenology of the pharmacodynamic effects, I now want to discuss what are the potential implications for us as clinicians here. That depends on a question what are the actual functions of the memory T-cells that are being manipulated.

In the physiological setting, memory T-cell are important in the prevention of infections. They are important in assisting B-cells for antibody responses to recall antigens so when we get reexposure to an antigen we have previously seen, the IgG responses are critically dependent on memory help.

Finally, they play a potential role in immune surveillance in conjunction with other cell types such as natural killer cells. That is in the

physiological setting. In the pathological setting, Dr. Adelman has already discussed data demonstrating that memory T-cells are important in the induction of a range of autoimmune disorders including psoriasis.

Over the next two or three minutes, I want to close by addressing what sets of data do we have addressing each of these points.

[Slide.]

First, the issue of infections and T-cell counts. In the randomized placebo-controlled studies, we divided patients into those that had counts below 250 versus those that had counts above 250 and quantified the patients that had infections after counts under 250. That number was 24 percent. Contrasting that to those that had infections when counts were above 250, 46 percent, the data suggest that lower T-cell counts do not predispose to infections. Now, this is a very preliminary look at this dataset. My colleague, Dr. Vigliani, who will discuss the safety profile with you, will go into this topic further.

[Slide.]

We have carefully studied immune-function tests in patients exposed to alefacept to try and

determine what evidence do we have for disturbance of normal immunity. To do this, we have used both cell-mediated--tested responses of cell-mediated immunity and responses to humoral immunity. Cell-mediated responses were most robustly addressed in the Phase 2 part of the program, specifically in the Phase 2 IV study that we discussed earlier, the Ellis and Krueger study. There, delayed-type hypersensitivity skin tests were carried out to a range of skin antigens using a CMI multitest.

Minor trends towards loss of response to some of the antigens was seen but, given the high false-positive and false-negative rate as well as the difficulty in conducting these types of studies, there are some important caveats when we review these data, and I would be happy to discuss those with you.

Contrasting that to the humoral responses, these were studied in the clinical study of 46 chronic-plaque-psoriasis patients of the type we treated during Phase 3. They were given either alefacept or placebo and immunized with two T-cell-dependent antigens. These are antigens that T-cells are critically involved in from mounting antibody responses to as documented in a range of

immunodeficiency studies in the literature.

The antigens were phi-X-174, a neoantigen that patients have never been exposed to where we tested both response when they were naive to the antigen as well as response after reexposure where we are specifically testing memory function. We also tested tetanus toxoid, an antigen that we are all immunized to and we have preexisting immunity to. Here the tetanus toxoid is a recall antigen and we are testing the memory component.

When we did these studies, we found that alefacept treatment did not abrogate anti-phi-X-174 or antitetanus antibody responses.

[Slide.]

To show you those data graphically, here are the phi-X-174 responses over time. The X axis is the dosing interval and follow up the Y axis is the mean antibody titer in log units. The primary exposure is associated with a brisk rise in antibody titer in both the alefacept and control groups which is overlapping. This demonstrates that naive T-cell function is intact in the alefacept-treated patients. They can respond to neoantigens.

The reexposure or the secondary

immunization is associated with a brisk rise in both groups again which appears to be entirely overlapping. The proportion IgG fraction in these patients receiving either alefacept or placebo was identical demonstrating that alefacept patients undergo changes in memory-T-cell counts but that these do not result in a change in their ability to mount antibody responses.

We have similar data where we demonstrated that patients had a twofold rise in antibody titer against tetanus toxoid that was identical between both alefacept and control groups.

[Slide.]

Finally, I want to turn to the issue of what about the pathological setting, given these manipulations of discrete T-cell subsets, do we have data validating the therapeutic rationale as originally proposed by Dr. Adelman. Here we have documented the response on CD4 memory T-cells and to what extent that correlated with the likelihood of patients achieving PASI 75.

Now, on the X-axis, you see this axis graded low to high where patients are divided in quartiles, where the reduction in CD4 memory T-cells is divided into four groups. Those in the

first quartile of the lowest group had the least CD4 memory T-cell changes. Those in the highest quartile had the greatest extent of CD4 memory T-cell changes. Those intermediate had intermediate changes.

Now, as you go from left to right, you can see the stepwise increase in the likelihood of response to PASI 75; 13, 23, 33 and 41 percent. These are encouraging data but they are somewhat indirect because we are looking for the surrogate whereas the site of action is really the skin lesion.

[Slide.]

To address that, Jim Krueger has conducted a study over the last eighteen months asking the question what do we understand about changes in T-cells in the skin and outcomes after a patient is treated with alefacept. Here are just some of his data. What you see here is a plot of the T-cell number at various time points for 21 patients pre-clin versus the change in epidermal thickness at those corresponding time points when the T-cell number was assayed.

You can see the data are tightly gathered. In fact, the r-value is 0.87. This suggests a very

tight correlation between the change in T-cell number in the skin associated with alefacept therapy and the therapeutic outcome.

The last two slides provide important data validating the therapeutic rationale as originally proposed.

[Slide.]

So I would like to close my presentation by summarizing that, for lymphocyte pharmacodynamics, both in Phases 2 and 3, we have demonstrated that alefacept treatment is associated with selective reductions of memory T-cells with a relative sparing of naive T-cells. There is a great deal of more data behind that bullet point and some of those are with Dr. Krueger from his studies where he has also demonstrated selectivity of changes in the skin versus blood with preference towards changes in the skin and also changes in discrete sub-subsets of memory cells, specifically those that are home to skin to mediate the disease versus those that reside in the central memory compartments. We can, perhaps, review some of those data in the Q&A.

With respect to the second point, we have demonstrated dose-dependent and gradual and

predictable changes during therapy. The findings are consistent and predictable throughout. There has been an increase in lymphocyte counts following cessation of therapy and the reductions in T-cell counts that we have seen have been correlated with efficacy as I demonstrated but have not predisposed to infections.

That is a suitable point to turn to the discussion of the safety profile and I will now ask my colleague, Dr. Vigliani, to come up.

Before she comes up, there is just one point I would like to address was the pharmacokinetics which I didn't discuss. The pharmacokinetics are very consistent for the IM and IV and there is as minor point of clarification. In one of the briefing documents, there were some placebo patients that were said to have alefacept in their circulation during the PK assays. Those patients have been revisited and we have provided data to the FDA that have resolved that, demonstrating that this was inference in the assay at baseline. Those were false positives.

So, with that, Dr. Vigliani, if you could--

DR. DRAKE: I would like to take the

prerogative of the chair. I have looked at your slides and the time left. So I just want us to the cognizant of your allotted time. We are a little bit--I don't know how you have divvied it up among yourselves, but if we could try to hold--the next two presenters please hold to the time schedule, we would be appreciative.

Thank you.

DR. VAISHNAW: Okay.

Clinical Safety

DR. VIGLIANI: Good morning.

[Slide.]

It is my pleasure to be here today to deliver the clinical-safety presentation.

[Slide.]

I will begin by defining the size and scope of the clinical-safety database. I will then review the most common and most serious adverse events. I will review all deaths and will then focus on the issue of malignancy and infection since these are important areas of interest with any new immunomodulatory therapy. Finally, since alefacept is a protein immunobiologic, I will discuss the issue of immungenicity.

[Slide.]

Let's now turn to the clinical-safety database. Within clinical-safety database are the 876 patients from the three placebo-controlled studies previously discussed. We have integrated the data from these three studies and done pooled analyses comparing event rates in alefacept-treated patients with event rates in placebo-treated patients.

The integrated analysis provides larger numbers of patients thereby increasing sensitivity for detection of trends not observed in individual studies. However, important differences by study occurring in the individual studies will be highlighted when relevant.

The total clinical experience that we are discussing today consists of 1157 chronic-plaque-psoriasis patients from all alefacept studies in which patients have received between one and five courses of treatment. The comparisons presented today will include the integrated placebo-controlled patient experience as well as the experience by course.

[Slide.]

When reviewing the placebo-controlled comparisons, keep in mind that there is significant

disparity in terms of the number of patients receiving alefacept and the number of patients receiving placebo. If we compare the patient years of exposure, as shown on the Y-axis, you can see that alefacept exposure is more than two times that of placebo exposure.

The person-year exposure is further magnified when considering the total alefacept people database. The higher person-year exposure in alefacept-treated patients increases the likelihood of capturing adverse events in these patients. Additionally, events of low frequency have an even lower likelihood of being observed in the placebo group.

[Slide.]

Let us now move to a broad safety overview of the placebo-controlled studies examining four categories of events; incidence of any adverse events, serious adverse events, discontinuations due to adverse events and deaths. Here we find that both alefacept and placebo groups are well balanced in each of the categories. There was one death in the alefacept group, a patient who committed suicide related to his long-standing skin disease.

[Slide.]

The safety overview by course provides a similar picture. If you look across the top of this table, you can see the number of patients exposed during each course. Upon review of the four categories, there is no broad evidence of cumulative toxicity based upon this top-level view of these important categories of events.

[Slide.]

If we now take a look at the most frequently observed adverse events, that is those seen at greater than or equal to 5 percent incidence in placebo-controlled studies, we see that 79 versus 83 percent experienced adverse events. The range of adverse events reported is typical for the population studied. There are no unusual or atypical events.

You can see that none of the adverse events occurred at a rate of 20 percent or greater. This speaks to the overall tolerability of alefacept and also speaks to investigators' ability to maintain the integrity of the blind during these studies.

When you compare the left-hand column to the right-hand column, you can see that the groups

are generally well-balanced. When we look at differences on the order of 5 percent or greater, we find only one event, chills, occurring in 1 percent of the placebo group and in 6 percent of the alefacept group. This is the one adverse event that has consistently been associated with alefacept exposure.

Chills were generally seen via the intravenous route of administration, were generally mild occurring early in the course of therapy and were not associated with fever or other symptoms and, importantly, did not result in discontinuation of study drug.

One category of adverse events not listed on this slide is injection-site reactions because they occurred at an overall incidence of less than 5 percent in the integrated database. They did, however, occur at a higher rate in the intramuscular Phase 3 study. However, they did not represent a significant tolerability issue.

[Slide.]

I would like to now consider serious adverse events. These events were largely considered serious based upon the regulatory serious based upon the regulatory definition of

serious and, in most cases, this was based upon the requirement for hospitalization.

[Slide.]

This table displays serious adverse events seen in more than one alefacept-treated patient in the placebo-controlled experience. The complete table can be found in your briefing document. Alefacept and placebo were well-balanced with 5 percent incidence of serious adverse events in each group.

The most frequently observed event was psoriasis which occurred in six patients in the placebo group and in two patients in the alefacept group. Serious adverse events observed both in alefacept and placebo included chest pain and pancreatitis. Some events show a slight imbalance with higher rates in alefacept-treated patients--for example, coronary-artery disorder, cellulitis and myocardial infarction.

This apparent imbalance may be explained, at least in part, by the fact that we have much greater alefacept exposure than placebo exposure and the number of events is small. Also note that numerous single occurrences of serious adverse events are not displayed in this partial table

accounting for the similar overall rates of serious adverse events between the two groups.

[Slide.]

The rates of serious adverse events did not increase with increased exposure in repeated courses. So if you look along the top in yellow, 5 percent in the first course and going down to 2 percent in the fifth course experience serious adverse events.

The range of adverse events seen were, again, typical for the population studied and didn't change significantly from those observed in the placebo-controlled studies. Considering some of the individual events noted at a higher rate in the placebo-controlled experience such as coronary-artery disease and cellulitis, none increased in incidence with further courses of therapy.

Importantly, when evaluating overall observed rates for events such as myocardial infarction and coronary -artery disease, the rates are consistent with the expected rates in the general population based upon available epidemiological data.

[Slide.]

I will now review the reported deaths

within the program. There have been a total six deaths in the alefacept program to date. The first four were detailed in your briefing document. Three of these occurred in patients on alefacept and one patient died prior to receiving study drug.

Two additional deaths have been reported since the briefing document and are listed below the line at the bottom of this table. Moving to the top of this slide, we see the suicide previously mentioned. This involved a 34-year-old man with a lifelong history of psoriasis and, unfortunately, a family history of suicide. His disease was featured prominently in his suicide note.

This case clearly illustrates the psychosocial impact that psoriasis has in this patient population. There were two deaths from myocardial infarction. Both were middle-aged men with multiple risk factors. While one occurred in a patient on alefacept, the other occurred prior to receipt of study drug.

These cases emphasize some of the comorbidities in the study population. The fourth patient died because of esophageal carcinoma resulting from Barrett's esophagus. The two

remaining deaths reported after your briefing document include a case of lung carcinoma in a heavy smoker and a patient with a history of seizures who died during a grand mal seizure in his sleep ten months after receiving study drug.

[Slide.]

Let's now move to a discussion of infections. In addition to collecting adverse events, investigators were required to perform an assessment of the patient for signs and symptoms and infection at each study visit. They were further required to record whether each adverse event represented a new or ongoing infection.

Now, this prospective collection of adverse events associated with infection facilitated the identification and analysis of these events. We have also analyzed the risk of infection in relation to reductions in T-cell counts.

[Slide.]

Looking first at infections that occurred at an incidence of 5 percent or greater in the placebo-controlled studies, 43 versus 45 percent in the two groups experienced an event associated with infection. There were only four events that

occurred at an incidence of greater than or equal to 5 percent. These include pharyngitis, nasopharyngitis or the common cold, flu-like symptoms and nonspecific viral infection.

As you compare placebo to alefacept for these four events, note that the groups are well-balanced leading to the conclusion that alefacept did not predispose to these common types of infections.

[Slide.]

Now let's look at whether any of these infections occurred at a higher rate in patients with low CD4 counts. During the pharmacodynamic part of the presentation, Dr. Vaishnaw showed you the top part of this table in yellow. Note that a lower proportion, or 24 percent of patients who had CD4 counts less than 250 developed an infection compared with 46 percent of those who maintained counts above 250.

The rest of this table illustrates the range of infections that were associated with low T-cell counts. As you scan through the events, note that there are no events suggestive of opportunistic infections or immunodeficiency. If you compare the incidences for these infections by

the CD4-count groupings, you see no significant imbalance.

We have analyzed rates of infections for different CD4 thresholds as well as CD8 thresholds and have found no correlation between the risk of infection or serious infection and reduction in lymphocyte counts. The same holds true if you look at data from the multiple course experience. This leads to the conclusion that alefacept-mediated reductions in lymphocyte counts do not predispose to infection.

[Slide.]

Now let's turn our attention to serious infections. Serious infections were observed at an equal rate of less than 1 percent in both alefacept and placebo groups. There were no atypical or opportunistic infections. This is the placebo-controlled experience. The data are similar across the multicourse experience as described in your briefing document. There were a total of 19 serious infections in the entire alefacept database. You may notice that skin infections were the most frequent category of infection in the placebo-controlled experience. Therefore, we will now look at this issue in greater depth focussing

on all serious skin infections in the entire 1300-patient database.

[Slide.]

This table displays the case details of all serious skin infections across the entire program. These are divided into skin infections and postoperative wound infections. Note that in almost all of the cases, there were significant risk factors which alone could account for the types of infections observed.

For example, several patients had diabetes mellitus and/or a disruption of the integrity of the normal skin barrier. The first patient, a diabetic, had a history of recurrent otitis externa. The second had manipulated a sty with resultant pre-septal cellulitis. The third had multiple cardiopulmonary medical problems and was treated for a presumed cellulitis, complicating peripheral edema and erythema surrounding a large psoriatic plaque.

Another patient with a history of arthritis had a small finger abscess following treatment of olecranon bursitis five months after study drug. Another developed cellulitis surrounding a Herpes simplex lesion near the eye.

Each of these patients had uncomplicated infections and responded to conventional therapy. Additionally, there was one case of cellulitis resulting from a large burn and a case of toxic-shock syndrome occurring two months after completing alefacept. This patient experienced the usual complications of toxic-shock syndrome but made a full recovery.

In addition, three postoperative wound infections were reported, one requiring debridement, repeated debridement after a rotator-cuff repair. This patient has since continued in retreatment studies without further incident.

The two others included a repair of an open and lacerated fracture of the tibia and a surgical infection following appendiceal rupture.

Note also that more than 50 percent underwent surgical procedures without such complications. In all cases, patients were treated with conventional therapies will full recovery. The majority of patients continued with treatment. There was no correlation between serious infection and reduction in CD4 counts.

I would like to take a minute to discuss the burn infection in greater depth as I feel that

it illustrates that maintenance of normal immune function almost certainly contributed to a favorable outcome in a high-risk patient. The patient was an obese diabetic man who dropped a hot radiator on his abdomen while maintaining his car sustaining a large abdominal burn measuring 18 by 24 centimeters.

Despite a significant disruption in the normal protective skin barrier in an area where wound healing would be otherwise compromised, this patient had an uncomplicated and brief admission to the hospital responding to a course of conventional antibiotics and topical treatments of his burn.

[Slide.]

So, with regard to infections, we can make the following conclusions. The incidence and nature of infections observed were similar between alefacept and placebo. Low CD4 counts did not appear to predispose to infections. There was no evidence of increasing risk of infections by course. The serious infections observed were uncomplicated in nature, clinical course and outcome.

Most importantly, we observed no opportunistic infections, no tuberculosis and no

deaths due to infection. Finally, there was no indication that the types of infections that would be suggestive of a T-cell immunodeficiency were observed in the association with alefacept therapy.

[Slide.]

So we have asked ourselves the question why is it that we haven't seen an increase in the risk of infection despite the significant T-cell effects of this drug. There are a number of possible reasons for this observation.

The first is that alefacept does not alter naive T-cells allowing patients to respond normally to new bacterial, viral and other antigens. The second is that the effect of alefacept against memory T-cells is only partial. The remaining T-cells appear to be sufficient to promote antibody responses as demonstrated in the immune-function study previously discussed.

Third, there is significant redundancy within the immune system with memory functions divided between a number of important subsets that include CD45RA-positive cells. We have also noted that patients with infection are able to mount increases in their lymphocyte counts. Given that only 3 percent of the T-cell pool resides in the

circulation with the rest residing in lymph-node tissue, maintenance of lymph-node integrity may also explain why T-cell function appears to be preserved.

[Slide.]

I will now turn to the topic of malignancy.

[Slide.]

The proportion of patients with a malignancy in placebo-controlled studies were less than 1 percent for placebo and 1 percent for alefacept. As expected in this population, the most common cancer was non-melanoma skin cancer. This categorization includes both squamous-cell carcinoma and basal-cell carcinoma.

One patient in the placebo and six patients in the alefacept group, less than 1 percent in each case, had skin cancers reported during these studies. Two events of carcinoma, both in the alefacept group, were cases of testicular cancer and renal-cell carcinoma.

The patient with renal-cell cancer was diagnosed with an 11-centimeter renal mass within three weeks of initiation of therapy making causality unlikely in that case. Prostate cancer

was seen in both groups. Finally, a single case of skin melanoma was reported in the alefacept group. This occurred in a patient with a history of PUVA and UVB exposure for 60 months who had two prior squamous-cell skin cancers. His lesions were excised after his fourth dose of study drug. There was no correlation between the development of any malignancy and low lymphocyte or CD4 counts.

[Slide.]

In the multicourse experience, we have had various additional malignancies reported as presented in this slide with no clear trend towards an increase in incidence with successful courses of exposure. I will not discuss each of these cases in detail today but would like to comment on a single case non-Hodgkins lymphoma that was just recently reported in one of our retreatment studies.

[Slide.]

This involved a 68-year-old female with a history of long-standing psoriasis for over 50 years who had previously been treated with methotrexate and PUVA in the remote past. After twenty doses of alefacept, she presented with an isolated 2-centimeter node below her jaw. She was

diagnosed histologically with follicular B-cell non-Hodgkins lymphoma.

Workup was negative for other lymphoid tissue or bone-marrow involvement. The histopathologic and molecular features of this tumor suggest that it represents a sporadic occurrence of lymphoma rather than the type of lymphoma seen in association with immunosuppression.

[Slide.]

To gain a perspective on the overall rate of malignancy and the rate of specific malignancies, we compared the observed rates in our trials with those cited in published literature. This slide illustrates that the overall rate of malignancy, including skin cancers, of 20 per 1000 person years is consistent with the expected rate of 29 per thousand person years in severe psoriasis patients. You will note the confidence intervals here.

[Slide.]

So,in summary, we have seen no evidence of an increase in the risk of malignancy in alefacept-treated patients. The predominant cancers we have seen, as expected, as skin cancers, mainly

squamous-cell and basal-cell carcinoma, and the observed rates in the database are within the expected rates reported within the literature.

[Slide.]

Now let's turn to the issue of immunogenicity. If we look at the incidence of antibody development, we see that the rate of anti-alefacept antibodies are 2 percent or lower both at baseline and after treatment with no increase in successive courses. Rates were slightly higher in the IM study in the range of 4 percent.

The titers of anti-drug antibodies seen in the patients that were positive were generally below 1 to 40 and did not amplify with repeated dosing. There has been no evidence of specific adverse safety outcomes associated with the development of anti-alefacept antibodies.

[Slide.]

Let's now summarize the safety findings. Alefacept has a favorable safety profile as demonstrated by evaluation of adverse events, serious adverse events, infections and malignancies in more than 1300 patients studied with up to five courses of exposure for up to three years. The incidence of adverse events and serious adverse

events was similar comparing alefacept to placebo.

There is no convincing evidence of an increase in the incidence of infection or malignancy or any relationship to lymphocyte reductions. Alefacept has low potential for immunogenicity.

[Slide.]

We are committed to understanding the long-term safety of alefacept and, to this end, approximately 800 patients are currently enrolled in safety-extension studies the data from which were summarized here today and continue to be collected. At present, we have over 400 patients who have received more than four courses of alefacept therapy to date.

However, in order to best understand the key long-term safety issues, we recognize that large numbers of patients treated for longer periods of time will need to be studied. We believe that the optimal method to study these issues is via an alefacept safety registry study powered to specifically evaluate increases in the risk of adverse events of interest specifically infections and malignancies.

We are currently working with experts in

the field in order to optimally design and effectively execute such a study.

[Slide.]

Today you have heard about the unmet need for new therapies in the treatment of chronic plaque psoriasis. I would like to conclude the clinical presentation by summarizing the important and unique features of alefacept.

Alefacept represents a novel approach to the treatment of chronic plaque psoriasis by selectively targeting memory T-cells which are believed to be among the key pathogenic mediators in psoriasis. The effects of alefacept on T-cells correlate with improvement in disease activity but are not associated with adverse safety outcomes.

A clinically meaningful benefit is appreciated by the majority of patients. Response is associated with significant duration of disease remission. Most importantly, improvement in disease activity is associated with improvement in the quality of life of patients treated. Alefacept is very well-tolerated.

These properties position alefacept as the first systemic disease-remittive agent for psoriasis without significant organ-system

toxicity. The risks and benefits of this therapy have been rigorously evaluated and we believe that they support the use of alefacept as a new treatment option for this severely underserved population.

I will now turn the podium over to Dr. Mark Lebwohl who will discuss the risks and benefits of alefacept from the treating physician's perspective.

Alefacept Risk Benefit Profile

DR. LEBWOHL: Thank you very much, Dr. Drake and members of the panel.

[Slide.]

I will try to catch us up.

DR. DRAKE: You know, Mark, thank you very much. The only thing standing between these folks and a bathroom break is you. Mark, I am just teasing you. I just want to tell you that we are glad to see you and we are glad you are here and please feel free to present your information.

DR. LEBWOHL: Thank you very much.

[Slide.]

In addition to my role as Chairman of the Department of Dermatology at Mt. Sinai, I see patients about thirty hours a week and so it is a

pleasure to be here to tell you a little bit about psoriasis and about my experience with alefacept. I will spend only a couple of minutes for the nondermatologist members of the panel showing you some pictures of psoriasis and telling you a little bit about the treatments we currently use and then I will go to the risk-benefit profile with alefacept.

[Slide.]

This is plaque psoriasis.

[Slide.]

You can imagine the impact that this has on the quality of life of these individuals that work at home, in their interpersonal relationships.

[Slide.]

Involvement of the hands and feet gets in the way of day-to-day activities.

[Slide.]

Again, you can imagine what this does to an individual self-image.

[Slide.]

This is just a sampling of the patients whom we treated in our alefacept trials.

[Slide.]

The negative impact on quality of life

that psoriasis has has been compared in a number of publications to congestive heart failure and diabetes and found to be comparable to the impact that those conditions have on patients with those diseases.

[Slide.]

Fortunately, we do have some excellent therapies. This is my most commonly used treatment which is phototherapy with ultraviolet B. It does have a number of drawbacks. First, it involves treatments three times a week for at least a few months a year, in many cases, for most of the year. Patients need to have access to therapies so someone who lives two hours from a phototherapy box won't be able to get this treatment.

And last, but not least, it doesn't work for everyone.

[Slide.]

PUVA is another superb treatment for psoriasis. It is dramatically effective and, of the treatments that are currently available, it is the only one that provides a durable duration of remission. It is associated with some of the same problems; frequent treatments, access to therapy, but also has been associated with the development

of squamous-cell carcinoma of the skin and, most recently, it has been suggested that malignant melanoma occurs in PUVA-treated patients as well.

[Slide.]

There are three oral medications for psoriasis. The first and oldest of these is methotrexate. It is associated with hepatic fibrosis which has led us to guidelines which call for routine liver biopsies in patients who are treated with methotrexate.

Now, routine liver biopsies, by themselves, have significant morbidity and even mortality and, in this study from the Mayo Clinic, a 21-year experience of over 9,000 liver biopsies, 1 in 300 had a significant bleed that required intervention, 1 in 1,000 patients, approximately died.

For that reason, rheumatologists, in their guidelines, do not call for routine biopsies of everyone who gets methotrexate but it is also clear that the frequency of hepatic fibrosis is substantially higher in psoriasis patients than in rheumatoid-arthritis patients for a number of reasons.

[Slide.]

That point is made by this patient, who is a patient of mine and, as you can see, does not have much psoriasis because he is now on cyclosporine for his liver transplant. Incidently, he used to work at Mercedes Benz and is very proud of his Mercedes scar.

I have, in my practice, patients who have either had liver transplantation because of methotrexate, died while waiting for liver transplantation because of methotrexate or are currently on transplant lists.

[Slide.]

Probably a more acutely serious side effect of methotrexate is the effect it has on bone marrow. Dermatologists are pretty good at prescribing this drug and we do warn our patients not to take other medications. But I can't tell you how often they do. Patients go to another physician, are given either an antibiotic or a non-steroidal antiinflammatory drug which raises the methotrexate levels and results in bone-marrow toxicity.

In this study from Ottawa, some rheumatologists looked at teaching records at two hospitals, teaching hospitals, and surveyed

physicians in the Ottawa area and came up with 15 cases of pancytopenia due to methotrexate. Of those 15, two died, one of them directly attributed to methotrexate.

[Slide.]

The second drug I would like to speak about is our oral retinoids. The main side effect of oral retinoids is teratogenicity. But the side effects that really keeps patients from taking this drug is hair loss. This woman had a full head of hair. Not only did she lose her scalp hair, she lost her eyebrows and eyelashes and looked like a chemotherapy-treated patient. This is a very unpleasant side effect.

In addition, there are number of mucocutaneous side effect; thin nail plates, sticky skin, cheilitis fissuring and chapping of the lips. Here you see pyogenic granulomas which are very painful. This patient had difficulty using his fingers or walking because of pain from the pyogenic granulomas. Hyperlipidemia is another side effect of retinoids.

[Slide.]

Lastly, cyclosporine is approved for the treatment of psoriasis. The main limiting side

effect--it has many side effects but the main limiting side effect has been nephrotoxicity. Essentially, if you give enough cyclosporine for a long enough period of time, the vast majority of patients will develop some kidney damage. As a result, our guidelines call for limiting cyclosporine therapy to one year.

[Slide.]

What does alefacept offer? You can imagine the improvement in quality of life that this patient had from the treatment he got but I would like to point out that, according to the protocol of this study, the bar that was set to define treatment success was 75 percent improvement in PASI score. This patient was a treatment failure.

As you can see, the patient only achieved 66 percent reduction in PASI score. It was 75 percent at two weeks. So, despite this benefit, this is called a treatment failure.

[Slide.]

Another patient who did not achieve 75 percent reduction in PASI score. Imagine the difference from here to here. That is a treatment failure according to the high bar that was set in

this study for defining treatment success.

[Slide.]

Another patient. Imagine calling this a treatment failure and imagine the impact this had on this patient's quality of life. This patient did not achieve 75 percent reduction in PASI score.

[Slide.]

Again, here; same story. I can show you photo after photo of these. This is another problem with the definition of treatment success. This patient achieved 75 percent reduction in PASI score but not until twelve weeks after the last dose. The primary endpoint was defined at two weeks after the last dose.

So I can show you many patients who met the endpoint at twelve weeks but didn't meet it at two weeks after.

[Slide.]

I am only going to show you two patients who did achieve PASI 75 to make two points. The first point is that this patient had a remarkable improvement but noticed that she improved even further twelve weeks after the primary endpoint. The second point that I would like to make is the duration of remission.

[Slide.]

Here is the patient at baseline. Here is two weeks after the last dose, dramatic improvement, clear twelve weeks after the last dose.

[Slide.]

Here is the patient twenty-three weeks and only a little over nine months after, you see the psoriasis coming back, nine months, but still, compared to her baseline, a dramatic benefit.

[Slide.]

Who should receive alefacept? First of all, I believe that it should be limited to patients who have substantial psoriasis. Patients who will have limited disease that would respond to topical therapy certainly would not be the patient I would put on alefacept.

In my practice, I will continue to use UVB before alefacept. I think that this is an old and safe and effective treatment. But, for some patients for whom it is impractical, or for patients who simply don't respond to UVB, I think that alefacept is a valuable addition.

As far as PUVA, I believe it should be used in rotation with PUVA. The toxicity, the

carcinogenicity of PUVA has clearly been related to the cumulative dose. If you can rotate patients from PUVA to other therapies, you can minimize that cumulative dose and, thus, minimize the risk of skin cancer.

As far as methotrexate and cyclosporine, given their known toxicities in my hands, I would prefer to use alefacept before methotrexate and cyclosporine.

[Slide.]

A couple of points about managing alefacept patients. First, it has been studied both IM and IV and I believe that both should be available, there are some patients who don't like needle sticks. If you use it IV, you can draw your blood through the same injection site that you give the intravenous infusion. But, more important, in patients who are covered head to toe, it is sometimes painful to go through a thick plaque and it may be practical, in some patients, to give it IV.

As far as monitoring, you have already heard the suggestion that CD4 counts be obtained every two weeks. Examining our patients is going to be very important because we are not going to

give this drug to patients who didn't respond in the past. So, for patients who do respond are the ones who are going to get future courses.

I would also say that if you look at the way this trial was designed, it was designed to maximize exposure. In real life, it will probably be given less often. If you look at the statistics, there was a twelve-week rest period. The large majority, in fact, I believe over 90 percent of responders, maintained their response at twelve weeks. We are not going to treat patients who are still clear. We are going to wait until their psoriasis starts to come back.

So I think that, in real life, it is not going to be given with just a twelve-week break. It is going to depend on the patient.

Last, but not least, as with any new drug, we are going to have to observe patients for as yet to be determined side effects that we have not seen in these initial studies.

[Slide.]

As far as overall benefit-risk ratio is concerned, long-term exposure will weigh heavily in the benefit side of this because, as I mentioned, it will not be given to patients who do not

respond. It will only be given in the future to patients who have responded in the past.

I would point out that, in the study, the majority of patients did respond. If you look at the PASI 50 scores, 64 percent of patients after two courses achieved PASI 50. After one twelve-week course, 56 percent achieved PASI 50. So the majority do respond.

This will reduce the risk part of this ratio because we can monitor lymphocyte counts. If they fall, we simply withhold the drug. The duration of remission weighs heavily on the benefit side because there are very few treatments we have that will give us this duration of remission.

Last but not least, I believe it is important that this drug be approved so that we do have an alternative to the hepatotoxicity of methotrexate and the nephrotoxicity of cyclosporine.

With that, thank you.

DR. DRAKE: You are amazing, Dr. Lebwohl. Thank you.

What I would like to do now--I am going to take the prerogative of the chair and I am going to shift the schedule just a tiny bit because I have