DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

BLA 125118 Abatacept, Bristol-Myers Squibb
proposed trade name Orencia proposed indication
for the treatment of moderately to severely
active rheumatoid arthritis

Tuesday, September 6, 2004

8:30 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Allan Gibofsky, M.D., J.D., Chair
Johanna Clifford, M.S., R.N., Executive Secretary

MEMBERS

J. Michael Finley, D.O.
Norman T. Ilowite, M.D.

CONSULTANTS (VOTING)

Janet Elashoff, Ph.D.
David T. Felson, M.D., MPH
V. Michael Holers, M.D.

PATIENT REPRESENTATIVE (VOTING)

Leona Malone

ACTING INDUSTRY REPRESENTATIVE (NON-VOTING)

FDA

Keith Hull, M.D.
Bob Rappoport, M.D.
Jeffrey Siegel, M.D.
Marc Walton, M.D., Ph.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

DR. GIBOFSKY: Good morning. I would like to welcome the Committee and guests to this open hearing of the FDA Arthritis Advisory Committee. My name is Allan Gibofsky and I will be serving as Chair of this session.

I would like to begin by having the members of the Committee introduce themselves starting to my right.

Introduction of the Committee

DR. RAPPOPORT: Good morning. My name is Bob Rappoport. I am the Director of the newly formed Division of Anesthesia, Analgesia and Rheumatology Drug Products. I am here today because this product, along with another of other biologics for the treatment of rheumatologic diseases, will be transferred to my division at the end of this month.

DR. WEISS: I am Karen Weiss. I am currently the Office Director of the Office of Drug Evaluation VI. It is the office that oversees all

the biological therapeutic proteins which, as Dr. Rappoport says, coming very shortly, will be transferred to other review divisions but currently my office still has oversight for the biological products.

DR. WALTON: I am Marc Walton. I am currently the Division Director of the Division of Therapeutic Biological Internal Medicine Products which is the division that currently has oversight over this product but we will be transferring it to Dr. Rappoport's division at the end of the month.

DR. SIEGEL: I am Jeffrey Siegel with the FDA, Division of Therapeutic Biologics. I am a clinical team leader.

DR. HULL: I am Keith Hull, a medical officer.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedar Sinai and UCLA.

DR. ILOWITE: Norm Ilowite, pediatric rheumatologist from Schneider Children's Hospital in New York.

DR. GIBOFSKY: Allan Gibofsky, Professor

of Medicine at Cornell University and attending physician-rheumatologist at Hospital for Special Surgery and New York Presbyterian Hospital.

MS. CLIFFORD: Johanna Clifford, FDA. I am the Executive Secretary to this meeting.

DR. FINLEY: Michael Finley. I am a rheumatologist, Associate Professor of Medicine, Western University of Health Sciences in Pomona, California, and attending rheumatologist at Arrowhead Regional Medical Center in Colton, California.

DR. FELSON: I am David Felson. I am a rheumatologist and Professor of Medicine and Epidemiology at Boston University.

DR. HOLERS: I am Michael Holers. I am a rheumatologist and Professor of Medicine and Immunology and Head of the Division of Rheumatology at the University of Colorado.

DR. PORTER: I am Roger Porter, twenty years at NIH, ten years at Wyeth including working on etanercept, now a consultant to the industry and the PhRMA representative for this committee today.

DR. GIBOFSKY: Thank you.

I would now like to ask Ms. Clifford to read the conflict-of-interest statement that affects this proceeding and the members of the Committee individually.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such as this meeting. Based on the submitted agenda 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 the conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants: Dr. V. Michael Holers for his employer's negotiations with a firm for a study of a competing product. The grant is proposed for

less than $100,000 per year; Dr. Norman Ilowite for consulting for a firm that developed and co-markets a competing product for which he receives less than $10,001 per year and for Speakers Bureau activities for a firm that co-markets a competing product for which he receives less than $10,001 per year.

In accordance with 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4), Dr. Allan Gibofsky has been granted full waivers for consulting for a competing firm on general issues for which he receives less than $10,001 per year, consulting and lecturing for competing firms on general issues for which he receives less than $10,001 per year and stock ownership in three competing firms, one worth from $5001 to $25,000 and the other two worth between $5,000 and $50,000.

Lastly, in accordance with 21 U.S.C. 355(n)(4), Dr. J. Michael Finley has been granted a waiver for ownership of stock in a sector mutual fund valued between $5,001 to $25,000. This de minimis financial interest falls under 5 CFR Part 2640.201 which is covered by a regulatory waiver

under 18 U.S.C. 208(b)(2).

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

We would also like to note that Dr. Roger Porter has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Porter was employed by Wyeth from 1992 to 2002.

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. GIBOFSKY: Thank you, Ms. Clifford.

At this point, I would like to ask Dr. Karen Weiss of the agency to make some opening remarks.

Opening Remarks

DR. WEISS: Thank you. My remarks will be very brief. First of all, on behalf of the FDA, I would like to welcome this committee. We are here to discuss Orencia or abatacept from Bristol-Myers Squibb. As you are probably aware, this is a new molecular entity with a new mechanism of action and, as such, we think it is very important to bring the issues out to this committee in an open discussion.

You will hear information about the efficacy data, the safety data, the various types of assessment tools that were used and we have a number of questions at the end of all the presentations for this committee to bring out and highlight many of those issues.

So, as the discussion proceeds, we will look forward to a very interactive day and advice

from this committee. Again, we think that the role you play is extremely important, particularly as we bring new products forward for treatment of rheumatoid arthritis.

Thank you.

DR. GIBOFSKY: Thank you, Dr. Weiss.

I would just echo those comments and point out that the discussion here today is going to be completely free and unfettered, without reference to any conclusions that may have been drawn in the lay or financial press earlier this morning and will involve a thorough review of issues relating to efficacy and safety of the agent under discussion today.

At this point, I would like to call upon Dr. Joy Williams from the agency to give us an overview of the drug abatacept for the treatment of rheumatoid arthritis, its product attributes and mechanism of action.

Dr. Williams.

Abatacept (CTLA4-Ig) for the Treatment of Rheumatoid Arthritis; Product Attributes

and Mechanism of Action

DR. WILLIAMS: Good morning.

(Slide.)

I would like to introduce you today to abatacept, the molecule. I will do this by mentioning a few key attributes of the abatacept drug product. I would also like to provide a brief summary of the mechanism of action as we currently understand it. I would comment that our understanding of the mechanism of action derives from numbers of--it is a fairly extensive literature in which CTLA4-Ig has been used and studied and the CTLA4-Ig used and commented upon in the literature derives from several sources, not all necessarily the BMF material.

(Slide.)

I would like to begin by commenting that the BLA for abatacept came to the FDA in a modular format meaning that, as different reviewable units were completed, they were submitted to the agency and, as product reviewers, as you can see on these slides, we were the last to receive our complete

reviewable unit that arrived at the end of March.

So we are still in the process of collecting and analyzing data. But what I can say at this point is that we have not encountered any issues in our review that we consider to be unresolvable.

As you can see at the bottom of the slide, the PDUFA action date or decision date for this product is the end of December of this year.

(Slide.)

I would also like to begin by acknowledging that this has very much been a multidisciplinary effort that has required collaboration among members of various review teams that you see listed here and has certainly benefited some critical input from division leaders and team leaders as well whose contributions have been invaluable.

Amongst the product reviewers themselves, I would like to mention that both members of the Division of Therapeutic Proteins as well as Monoclonal Antibodies, our sister division, have

worked in the review of this product.

(Slide.)

I will begin first by crediting, by thanking, Bristol-Myers Squibb for allowing me to use this very lovely diagram of the abatacept molecule. As you are probably all aware, this molecule function as a T-cell inhibitor, and I will allude to that in more detain in further slides.

As you can see here, the abatacept molecule is a homodimer. Each member of that dimer, or each of the two chains that compose the dimer, are derived from a genetic fusion of human CTLA4 extracellular sequence that has been fused to human IgG1 Fc sequence to create the entire molecule.

The members of the dimer are held together by a single disulfide bond that is actually in the CTLA4 portion of the molecule. You can see that it is a glycosylated molecule and the sites for glycosylation are indicated at appropriate asparagines and serines in this diagram. I would like to mention at this point that, in the context

of our review, we are focusing to ensure consistency across both the CTLA4 portion of the molecule as well as the Fc portion of the molecule. We consider both of these to be critical components to how this molecule behaves in vivo and in the clinic.

(Slide.)

The abatacept molecule is derived from a culture of Chinese-hamster ovary cells. After a series of purification steps and viral clearance steps, the molecule is processed for final formulation as a sterile lyophile. It is supplied and packaged as a lyophile. It is reconstituted upon administration.

I should also comment that the abatacept is packaged with a non-siliconized syringe and will be distributed in this fashion.

(Slide.)

As I alluded to just a moment ago, I will tell you a little bit more about what we understand about how abatacept works. I think to appreciate the molecular action of this molecule, it is

necessary to just review briefly certain aspects of T-cell activation as we understand them.

For a T-cell to be productively or optimally activated requires interactions with antigen-presenting cells as I have illustrated here on this slide. What you can see happening here, and what we understand about T-cell activation, is that it requires not only a signal through the T-cell receptor when it recognizes cognate antigen but it is critically dependent as well on co-stimulatory signals.

Probably the best well-characterized and perhaps, in some ways, the most potent of these co-stimulatory molecules is the CD 28 molecule on T-cells. When it interacts with B7 on antigen-presenting cells, a co-stimulatory signal is initiated. This is very critical in order to modulate and, in a sense, optimize the immune response for whatever pathogen has been encountered.

Now, not long after this co-stimulatory pathway was elucidated, it became clear that this

might represent a potent way in which one could interfere with unwanted activation of T-cells if there were a way to interrupt this pathway.

Not long after that realization was made, the mechanism by which this might be accomplished became evident with the discovery of a second receptor of the B7 molecules; namely, CTLA4. CTLA4 is another surface receptor expressed on T-cells but it can interact with B7 with 10 to 20-fold higher acidity than CD 28 does. You can already imagine that it represents a good way to outcompete the CD 28 signal.

It was also realized that a way to harness the power of CTLA4 to do this would be to create a soluble form of the molecule.

(Slide.)

So that was done. What you can see here, and essentially this is the genesis of the abatacept molecule. Investigators took the extracellular sequence from the CTLA4 molecule and appended it, or genetically fused it, to the Fc region of some human IgG1 and, in doing so, now

have created a stable and soluble molecule. Furthermore, the presence of the Fc region allows for ease of purification of this molecule.

(Slide.)

As I am showing you here in this slide, as was anticipated with the genesis of this molecule, it can, in fact, be used to block T-cell activation. Both in vitro and in vivo models have shown that it is a very potent T-cell inhibitor and immunosuppressant. So it acts not only to directly, in a sense, inhibit T-cells by blocking the interaction with CD 28, as you see here in this cartoon but, in doing so, prevents activation of T-cell proliferation, cytokine production, et cetera, but, also important to note, that it can, in a sense, act indirectly to interfere with other T-dependent activities such as the production of T-dependent B-cell antibodies.

So while this cartoon illustrates what I think is the best-understood mechanism by which CTLA4-Ig may interfere with T-cell inhibition; i.e., by directly interfering with the capacity of

that CD 28 signal to signal to the T-cell.

(Slide.)

It has recently become appreciated that there are other mechanisms as well by which CTLA4 may help to create a T-cell-suppressive environment. One of those mechanisms is illustrated here on this slide. In the past couple of years, a number of labs have determined that, when B7 molecules are engaged by CTLA4-Ig and, interestingly, also by CTLA4 expressed on the surface of T-cells, a signal through the B7 molecule, itself, can be initiated.

One of the results of this signalling through B7 is the generation of an enzyme that can catabolize tryptophan. It turns out that activated proliferating T-cells are somewhat uniquely dependent on a good source of tryptophan in the environment so, when that is depleted, a T-cell-suppressive environment is, in essence, produced therefore, again, inhibiting T-cell activation.

What is sort of interesting about this

model is it means that subsaturating levels of CTLA4-Ig might useful in creating T-cell-suppressive environment.

(Slide.)

We would also like to posit that presence of the Fc portion may, as well, serve to create an immunosuppressive environment perhaps by targeting B7-expressing cells for destruction or clearance by Fc-receptor-bearing cells in the body.

As I mentioned some slides ago, activation of T-cells depends on encounters with B7-expressing antigen-presenting cells. So, if you get rid of those cells, again you are helping to promote T-cell-suppressive environment. Finally, although not put here on the slide, B-cells, themselves, can express FC receptors engagement of which, under certain circumstances, can dampen B-cell responses as well.

(Slide.)

So, taken together, it has become clear from the literature that there are a number of ways in which CTLA4-Ig may act to create a

T-cell-suppressive environment. But I think no discussion of the mechanism of action of this drug could be considered complete without mentioning that there may be certain circumstances under which the presence of CTLA4-Ig could exacerbate autoimmune disease in a somewhat paradoxical fashion.

(Slide.)

I think our major concern with regard to this potential activity has to do with T-regulatory cells. I am sure everyone in the room has heard a lot about these cells in the past couple of years and I think most immunologists have come to accept that these are cells that are very critical in creating and acting in a dominant fashion in the periphery to suppress potentially autoreactive T-cells.

This is certainly evidenced by the fact that, in animal models and mouse models and, unfortunately in humans as well, where the genesis of these cells has been inhibited by various means, individuals who lack these T-regulatory cells

succumb to very aggressive autoimmune disease. So there is really no doubt that these cells are very important.

(Slide.)

For our purposes, I think it is interesting to understand that these cells are uniquely dependent on CD 28 B7 in their action not only for their genesis in the thymus but for their maintenance in the periphery as well. That is illustrated here on these two slides.

I am showing you on the left some data from my own work in which I have shown the that absence of B7 in B7 in knockout mice means that you have a substantial decrease of these T-regulatory cells in the thymus. I would mention that Jeff Bluestone's lab and Al Singer's lab have demonstrated very similar things in CD 28 and B7 knockout mice.

Interestingly, again, on the right, you can see, in some work from Jeff Bluestone's lab, that the treatment of mice with CTLA4-Ig for a period of ten days leads to a substantial decrease

of these regulatory cells in the periphery.

So I think it is important to understand that this can happen. Certainly, there are inbred strains of mice that, paradoxically, in the absence of B7 and CD 28 which was expected to ameliorate disease, in fact, autoimmune disease in the case of the NOD mice, which are susceptible to diabetes, autoimmune disease is exacerbated and the underlying reason is believed to be, again, a decrease or absence of these T-regulatory cells.

Our concern here may or may not be so much for patients who are taking CTLA4-Ig and already immunosuppressed but, were it to be given to pregnant mothers, our concern certainly exists for the developing fetus in whom, as I have showed you here on the left side, there is some reason to be concerned that the presence of CTLA4-Ig could have detrimental effects on the development of appropriate immuneregulatory mechanisms within that fetus.

(Slide.)

Finally, another mechanism that needs to

be considered, the presence of soluble CTLA4-Ig will inhibit not only the interaction of CD 28 with B7 but the interaction of CTLA4-Ig with B7. What I didn't tell you when I introduced it is CTLA4, on the surface of T-cells, is that its purpose there seems to be to deliver a negative signal to the T-cell. So is it sort of the counterpart of CD 28 which is a positive signal. CTLA4 signals serve to dampen or attenuate T-cell responses. So, obviously, by having CTLA4-Ig in the picture, that natural termination mechanism, attenuation mechanism, is now disrupted.

Again, it may not be a problem in people who are already immunosuppressed because of the CTLA4-Ig, but were patients receiving CTLA4-Ig to develop antibodies to the CTLA4 portion of the molecule, this would not only mean that the drug, itself, would not function in those individuals. It could compromise the functioning of their own endogenous CTLA4-negative regulatory system.

(Slide.)

So, finally, I would like to close by just

putting here this slide for you summarizing what we understand currently regarding the immunosuppressive activities of CTLA4-Ig but just wanting to mention and put on the table that there are certainly aspects of the molecule which could exacerbate autoimmunity and consequently the successful functioning of this molecule in the clinic will require that those mechanisms which immunosuppress dominate over those which could exacerbate autoimmunity. I think you will hear quite a bit about how it actually has performed in the clinic in the talks that follow mine.

But, hopefully, now I have introduced you to the molecule and we will carry on from here.

DR. GIBOFSKY: Thank you. Are there any questions? I actually have one. You glossed over the issue of administration of CTLA4-Ig to the non-obese diabetic mouse. One of the issues that we are going to be discussing later under Section 5.11(1) are the special safety studies of abatacept in diabetic patients.

Could you review that and perhaps amplify

a little bit more your comments on the administration and the effect in the NOD mouse?

DR. WILLIAMS: Sure. If I remember that literature correctly, and I know Jeff Bluestone has dealt for many years with that model and then with the effects of costimulation in that model where initially it was expected that if one blocked the CD 28 B7 pathway, that the disease would be ameliorated in these animals.

What, instead, he discovered, and here I will comment that I am doing my best to recollect what he did in the case of using CTLA4-Ig to promote disease and best characterized with his work in CD 28 knockout animals where he has clearly shown a role for potentiating disease in these animals and to show that it was likely due to a decrease of regulatory cells because, when he transferred in regulatory cells from a wild-type sibling, for example, disease was lessened in those animals.

The slide I showed you here with the use of CTLA4-Ig to decrease regulatory cells in the

periphery of animals was actually from a separate study he did just trying to understand what the role of CD 28 B7 was in maintaining regulatory cells in the periphery, whether it was a signal unique to CD 28 that was generated that was required to keep those cells alive or whether it worked indirectly through CD 28 to upregulate to IL2 production. So they were two separate studies. But I believe that he found the treatment of CTLA4-Ig in NOD mice also exacerbated disease. I don't know if that helps.

DR. GIBOFSKY: Dr. Holers.

DR. HOLERS: I would actually like to thank you for bringing a contemporary view of CTLA4-Ig and immune regulation into this discussion because I think that is, from the immunologist's standpoint, very important.

I have two questions; one is you commented on the FC-receptor-binding capability of the molecule. Has anything been done--I couldn't find this in the documentation--to alter its complement-fixing activity?

DR. WILLIAMS: Yes, and that is actually why I didn't put it on the diagram. But Bristol-Myers Squibb has characterized that aspect of the molecule and it appears that it does not fix complement. So that is the mechanism by which it would not function.

DR. HOLERS: The issue about potential fetal effects is largely done with knockouts. Are you aware of any studies that have been performed where CTLA4-Ig has been given to a mother rodent and there has been alteration of thymic tolerance in the fetus?

DR. WILLIAMS: I am not aware--we have started combing the literature for that sort of thing and I am not aware of a systematic study done to address that particular issue although I believe that CTLA4-Ig can pass through the placenta and get access to that fetus. So that is a concern.

DR. HOLERS: Thank you.

DR. GIBOFSKY: Are there other questions for Dr. Williams?

Thank you very much.

Before we hear from the sponsor, I would like to welcome our patient representative and ask her to please introduce herself for the other members of the committee.

MS. MALONE: Hi. My name is Leona Malone. I am from Palm Beach Gardens and I am the patient representative. I am a licensed clinical social worker.

DR. GIBOFSKY: Thank you very much.

At this point, I would like to call up the representatives of the sponsor, Bristol-Myers Squibb, who will have 60 minutes to make their presentation divided up among several members of their group however they see fit. Then we will begin our question period to them.

Sponsor Presentation -- Bristol-Myers Squibb

Introductory Remarks

DR. DANIELS: Dr. Holers, we actually do have some information on the thymic development in pups, in animals, where the mothers have been administered CTLA4-Ig so we can, perhaps, shed some light on that.

DR. HOLERS: I thought so.

(Slide.)

DR. DANIELS: Thank you, Mr. Chairman, members of the Advisory Committee. Good morning. My name is Brian Daniels. I am a Senior Vice President of Global Clinical Development at Bristol-Myers Squibb.

As a rheumatologist, it is a privilege to be part of today's presentation on abatacept. One of the attractions of rheumatology, to me, is that the recent advances in molecular and cellular biology have made possible the development of important new therapies for our patients. Abatacept represents such a therapy. It offers patients and physicians a new and much-needed option in the treatment of rheumatoid arthritis.

As a chronic and debilitating disease, rheumatoid arthritis affects approximately 2 million people in the United States. It has a profound impact on both patients and their families. In about one year of diagnosis of rheumatoid arthritis, one in ten patients stop

working and, by ten years, about half are disabled.

Despite the recent advances in the treatment of rheumatoid arthritis, significant unmet medical need remains. At least 30 percent of patients fail to respond to therapy as assessed by ACR 20 criteria. Others respond initially but lose efficacy over time and many experience treatment limiting toxicities.

Abatacept has been developed to address these unmet needs. However, all new therapies must provide significant benefit with acceptable risk. The benefit and risk data presented today reflect the known information about abatacept in both the clinical and non-clinical settings.

Abatacept's clinical benefits are based on its mechanism of action. Abatacept selectively inhibits specific T-cells thereby reducing their proliferation, the elaboration and numerous mediators of inflammation and the production of autoantibodies such as rheumatoid factor, the clinical benefits of this mechanism of action, as seen in the improvement in patient signs and

symptoms of their rheumatoid arthritis, their physical function, overall quality of life and the inhibition of structural damage progression.

To fully characterize these benefits, Bristol-Myers Squibb conducted an extensive phase II/Phase III clinical program treating over 2600 patients with abatacept. Abatacept is the first molecule to demonstrate benefit both in patients with active disease on TNF-blocking agents as well as active disease in methotrexate therapy.

The potential risks for abatacept are infection and malignancy as with any immunomodulatory therapy. In addition, as a protein therapeutic, there is a potential for hypersensitivity reactions. Our clinical program identified an increase in infection, both serious and non-serious, with abatacept therapy. In a large part, these infections are rarely identified and managed by the treating physician.

The risk to malignancy appears similar to the that of the RA patient population in general. Serious infusion reactions are rare.

Investigational clinical trials, however, represent just one stage in the overall assessment of benefit and risk. The complete profile of any new molecule is only understood after its use in the marketplace. BMS is, therefore, characterized to continuously characterize abatacept's therapeutic benefit and potential human risk throughout its life cycle. This will be accomplished through a thorough, post-approval, pharmacovigilance program that you will hear about later this morning.

We appreciate the opportunity to be here and to discuss the abatacept program. Now I would like to introduce Dr. Tony Waclawski, Executive Director of Regulatory Affairs, who will present a regulatory history of abatacept and introduce the rest of today's speakers.

Tony?

Introduction to the Product

DR. WACLAWSKI: Good morning.

(Slide.)

The purpose of our presentation today is

to present data to show that abatacept is a safe and effective therapy for the treatment of rheumatoid arthritis.

(Slide.)

Abatacept is a new therapy for RA with a new mechanism of action and offers patients with rheumatoid arthritis an alternative to existing therapies. It is the first in a new class of drugs called the selective T-cell costimulation modulators designed to modulate the activity of T-cells in autoimmune diseases.

Abatacept is a fully human fusion protein. It consists of the extracellular domain of human CTLA4 liked to the modified Fc portion of human IgG1. It is administered as a 30-minute infusion each moth at a dose approximating 10 milligrams per kilogram. The proposed trade name is Orencia.

(Slide.)

This is the proposed indication. Orencia is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage and improving

physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs such as methotrexate or TNF-blocking agents. Orencia may be used in combination with methotrexate or other nonbiologic DMARD therapies.

(Slide.)

These are the milestones in the regulatory history. Two designations are intended to speed the development and the review of new drugs that offer patients with ummet need a promising new therapy. They are the Fast Track Development Program and the use of the Continuous Marketing Application Pilot Program.

(Slide.)

The core clinical program includes these studies. There were three phase II studies, a dose-finding study, a larger dose-ranging study and a study of abatacept used in combination with etanercept. These studies were designed to identify an appropriate dose of abatacept for phase III and to provide preliminary information on the

efficacy and safety of abatacept.

There are three large phase III studies, one in patients not responding adequately to methotrexate, the other in patients not responding adequately to TNF-blocking agents. These studies were double-blind, placebo-controlled and designed to confirm the efficacy and safety of abatacept using accepted clinical endpoints for studies in rheumatoid arthritis.

The third phase III study is also a randomized, double-blind, placebo-controlled study. It was designed specifically to assess the safety profile of abatacept in patients taking a variety of concomitant therapies. This study had few exclusions and studied abatacept under conditions intended to mimic clinical practice.

(Slide.)

In the presentations that follow, key efficacy endpoints are presented from the studies shown here in yellow. These studies are at least six months in duration and tested abatacept at the dose approximating 10 milligrams per kilogram.

(Slide.)

Our core safety database is made up of these studies. Each of these is at least six months in duration.

(Slide.)

The data presented today reflect an experience in over 1900 patients taking abatacept with more than 1300 of them taking abatacept for at least one year in placebo-controlled trials. Today, over 2,000 patients are taking abatacept in ongoing, open-label extensions to our phase II and phase III program.

Combining the double-blind and open-label experience, the data presented today reflect an experience in over 2600 patients which translates into 3800 patient years of experience.

In addition to these ongoing studies, we have a pharmacovigilance plan that includes large post-authorization studies. They will monitor the long-term safety of abatacept in over 5,000 patients. Overall, the data we are presenting today show that abatacept can offer patients with

rheumatoid arthritis a new therapy to help them with this debilitating and painful disease.

(Slide.)

This is our agenda for the rest of the presentation. Dr. Vratsanos, a rheumatologist from our clinical team, will present the clinical efficacy data. He will begin his presentation with a brief overview of the mechanism of action.

Dr. MacNeil, the lead physician from our abatacept team, from our Pharmacovigilance Department, will present the safety data.

Dr. Daniels will provide some closing comments. I will then return and moderate the question and answer session.

(Slide.)

I would now like to move on to the efficacy presentation. Dr. Vratsanos?

Efficacy Presentation

DR. VRATSANOS: Good morning, Mr. Chairman, members of the committee and FDA.

(Slide.)

Abatacept has a unique mechanism of action

that selectively targets T-cell activation. Its efficacy was first investigated in two phase II trials in patients with an inadequate response to DMARD therapy. Two phase III pivotal trials were then conducted to definitively assess its efficacy in patients with active RA despite methotrexate or patients with active RA despite anti-TNF therapy, respectively.

(Slide.)

Activated T-cells play an important role in RA. Abatacept is a selective costimulation modulator that inhibits T-cell activation. Full T-cell activation usually requires at least two signals. The first signal, shown here in green, involves the recognition of antigen delivered by an antigen-presenting cell, or APC, to the T-cell. Signal 2, shown in purple, involves the iteration of the CD 80, CD 86, ligands on the APC with the CD 28 counter-receptor on the T-cell. Abatacept inhibits T-cell activation by binding specifically with high avidity to CD 80, CD 86, on the APC.

(Slide.)

Activated T-cells interact with macrophages and fibroblast-like cells which then produce proinflammatory cytokines such as TNA alpha and interleukin 6. They also produce destructive proteolytic enzymes such as matrix metalloproteinases. In addition, T-cells provide key signals for the activation, proliferation and differentiation of B-cells into autoantibody-producing cells.

Therefore, abatacept, by inhibiting T-cell activation, would be expected to attenuate multiple inflammatory pathways in RA.

(Slide.)

Nonclinical and in vitro studies were conducted to assess the mechanism of action of abatacept. The results of these studies suggested that it would decrease both T-cell activation and proliferation in patients with RA. Consequently, it would also reduce the production of proinflammatory cytokines and autoantibodies. In these studies, we observed no depletion of T-cells or other leukocytes.

(Slide.)

Dose selection for the phase III study was based upon the results from two phase II trials.

(Slide.)

A small, initial dose-finding study of abatacept monotherapy, IM103-002, was conducted in patients with active disease despite DMARD therapy. Based upon the human in vitro and nonclinical data, we chose doses of 10, 2 and 0.5 milligrams per kilogram for this 3-month placebo-controlled trial.

The 2 and 10 milligram per kilogram doses produced higher ACR 20 responses than placebo but the 0.5 milligram per kilogram dose did not.

A larger dose-ranging study, IM101-100, was then conducted to further assess the efficacy of the 1 and 10 milligram per kilogram doses. These doses were added on to methotrexate in patients with active disease despite methotrexate therapy.

(Slide.)

Only the 10 milligram per kilogram dose demonstrated statistically significant efficacy

relative to placebo. It also produced higher ACR 50 and ACR 70 responses. Both doses exhibited a similar safety profile to placebo. Therefore, a fixed-dose approximating 10 milligram per kilogram was carried forward into phase III and was used for the extension period of this phase II trial.

(Slide.)

A large group of patients have moderate to severe RA despite treatment with methotrexate. In addition, the advent of new therapies for RA has led to the emergence of a new patient population with ummet medical need. These patients have active RA despite treatment with anti-TNF therapies. The novel mechanism of action of abatacept offered an opportunity to explore its efficacy in both of these patient populations. Our phase III program included two pivotal efficacy trials, one in each of these patient populations.

(Slide.)

Patients with an inadequate response to methotrexate were studied in a twelve-month randomized double-blind comparison of abatacept

versus placebo. A fixed dose of abatacept approximating 10 milligram per kilogram was given intravenously over 30 minutes on Day 1, Day 15, Day 29 and then monthly thereafter.

Patients could not receive DMARDs other than methotrexate during the first six months or increase their methotrexate dose during this time. However, they could do so after six months at the discretion of the investigator. The sequential co-primary outcomes for the study were the ACR 20 response rate at six months, improvement in physical function at one year and the change in the radiographic erosion score also assessed at one year.

(Slide.)

Most patients in each group had long-standing seropositive RA for about nine years. They received a dose of methotrexate on average about 16 milligrams considered to be effective in clinical practice.

(Slide.)

Patients in both groups had high disease

activity at baseline as evidenced by their joint counts, both tender and swollen, HAQ disability scores, C-reactive protein and DAS 28 scores. Over 99 percent of patients in each group had erosions at baseline.

(Slide.)

About 90 percent of patients in the abatacept group completed the one-year double-blind period. There were fewer discontinuations overall in the abatacept group, 11 percent versus 26 percent. The rate of discontinuations due to adverse events was higher in the abatacept group. The major difference between the groups was in the rate of discontinuation due to lack of efficacy, 3 percent versus 18 percent, respectively.

(Slide.)

Abatacept was significantly more effective than placebo in inducing an ACR 20 response. Statistically significant efficacy was observed by Day 15, the first visit after the initial dose, and was sustained for one year. In this intention-to-treat analysis, all patients who

discontinued were considered to be nonresponders.

(Slide.)

Efficacy in inducing a more substantial clinical response, the ACR 70, was also observed. Statistically significant efficacy was observed by Day 85 and was sustained for one year. About 30 percent of patients on abatacept achieved an ACR 70 at one year. Abatacept was also significantly more effective in inducing an ACR 50 response.

(Slide.)

Two other measures of efficacy are the major clinical response and the proportion of patients with either no tender or swollen joints after treatment. The left panel shows the major clinical response at one year. This represents the proportion of patients who achieved an ACR 70 response for at least six consecutive months during the trial.

14 percent of abatacept-treated patients achieved a major clinical response versus two percent of placebo-treated patients. The right panel shows the proportion of patients with either

no swollen or tender joints at one year. 18 percent of patients treated with abatacept had no swollen joints at one year versus 4 percent of placebo-treated patients. The results were similar for the proportion of patients with no tender joints.

(Slide.)

The treatment effects for the ACR 20 response rate in different subgroups are shown here. Equivalent efficacy to placebo is indicated by the dashed vertical line through zero. Greater efficacy compared to placebo is shown to the right. The yellow mark is the ACR 20 response rate in the abatacept group minus the placebo group. The green bars indicate the 95 percent confidence interval for the difference between the two groups.

The treatment effect for abatacept was consistent in all subgroups analyzed including age, gender, body weight, rheumatoid factor status and disease duration. Additionally, multiple sensitivity analysis for this outcome also demonstrated that abatacept was more effective than

placebo.

(Slide.)

The efficacy of abatacept in inhibiting the progression of structural damage was assessed using the Genant modification of the Sharp scoring system. Radiographs were obtained at baseline and at one year in 586 patients which comprised about 90 percent of all randomized patients. This was the dataset for the primary statistical analysis. The radiographs were independently scored by two radiologists who were trained and who were blinded to both the sequence of the films and treatment allocation.

Since radiographic data are known to be highly skewed, we compared the distribution of changes from baseline using nonparametric methods for the prespecified primary and key secondary analyses. This is in accordance with recent published literature. We also compared mean and median changes from baseline.

(Slide.)

The Genant modification of the Sharp

scoring system has been validated and has been demonstrated to be both reproducible and sensitive to change. It has been utilized to demonstrate efficacy in retarding structural damage for FDA-approved products. It assesses joints in the hands, wrists and feet for both erosive damage and joint-space narrowing. The erosion scores and joint-space-narrowing scores are weighted equally in this modification of the sharp system.

Fourteen joints in each hand six in each foot are scored for erosions. Conversely, 13 areas in the hands and six in each foot are scored for joint-space narrowing.

(Slide.)

These results are based on the analyses from the 586 patients who had both baseline and follow-up films. The mean change from baseline for the erosion score, joint-space-narrowing score and total score were all statistically significantly lower in the abatacept group.

(Slide.)

The median changes for the erosion score

and joint-space-narrowing score was 0 in the abatacept group. Patients on abatacept had a lower median change in the total score, 0.25 versus 0.53 units. However, comparison of median changes gives limited information about the overall population and about the magnitude of change in each patient. Therefore, we compared the distribution of changes between treatment groups.

(Slide.)

We first show here the changes for the patients on placebo on background methotrexate from this trial. We use a cumulative distribution plot to better visualize the data. This type of plot allows one to visualize all of the data including all outliers.

Approximately 40 percent of patients had no change from baseline. However, about 55 percent had an increasing score at one year suggesting disease progression. Conversely, a much smaller proportion, about 5 percent, had a lower score at the end of one year compared to baseline. Therefore, the distribution of changes from

baseline is skewed towards those with an increasing score and this is where inhibition of structural damage can best be assessed.

(Slide.)

This plot shows a comparison of the distribution of changes now between the two treatment groups. Differences between abatacept and placebo are best visualized in the right side of the figure. The abatacept curve in yellow is shifted downwards relative to the placebo group suggesting a lower magnitude and likelihood of an increase in score.

The prespecified primary and key secondary analyses were comparisons of the entire distribution of changes between the two treatment groups. The difference between the groups was statistically significant for the erosion score, the joint-space-narrowing score and for the total score.

Efficacy was also observed in multiple subgroups including the patients at highest risk for radiographic progression. Collectively, these

data demonstrate that abatacept, in combination with methotrexate, significantly inhibited the progression of structural damage.

Patient-reported outcomes such as improvement in physical function are also important in evaluating the efficacy of any new anti-rheumatic therapy.

(Slide.)

The proportion of patients with improvement in physical function was assessed using different numeric criteria for what constitutes meaningful improvement. An improvement of 0.3 was prespecified for the primary analyses. Abatacept was significantly more effective than placebo regardless of the criterion used.

(Slide.)

Significant improvement in physical function was observed by Day 57 or two months after starting therapy and was sustained for one year. About 60 percent of patients on abatacept had improvement in physical function at one year. Subgroup analyses similar to those presented for

the ACR 20 also demonstrated that abatacept was more effective than placebo in improving physical function.

(Slide.)

Data showing that improvement in physical function observed at one year is sustained for at least two years comes from the extension period of the phase II trial. Long-term data using an as-observed analysis are shown in the top row. This is typically how the data are presented at scientific meetings and in publications.

55 percent of patients had improvement in one year and this was sustained at Year 2 and Year 3. In addition, we did a more conservative analysis where all patients who dropped out were considered to be nonresponders. We measured physical function in the 84 patients initially randomized to 10 milligram per kilogram who opted to enter the long-term extension.

Overall, the proportion of patients with improvement in physical function remained relatively stable over time, 55 percent at one

year, 46 percent at two years and 42 percent at three years.

We also asked if the 46 patients in the 10 milligram per kilogram group who had improvement at one year sustained that improvement over time. 67 percent of that patient population maintained that improvement at Year 2 and 57 percent maintained that improvement at Year 3. Collectively, the double-blind and long-term data indicate that improvement in physical function is sustained with abatacept.

(Slide.)

Another important patient-reported outcome is quality of life. The mean improvement from baseline was significantly greater for the abatacept group for the physical-component score of the SF-36, shown in the left panel, and the mental component score of the SF-36 shown on the right.

(Slide.)

Mean changes for each of the eight individual domains of the SF-36 were compared. Abatacept was significantly more effective than

placebo in improving each of the eight dimensions of quality of life captured by that SF-36. The treatment effect for abatacept was consistent across all eight domains.

(Slide.)

The second pivotal trial in our phase III program was a study of patients with an inadequate response to anti-TNF therapy.

(Slide.)

We conducted a six-month randomized double-blind comparison of abatacept versus placebo in patients with an inadequate response to either etanercept or infliximab. Adalimumab was not approved at the time the study was initiated. Some patients were still on anti-TNF therapy at the time of enrollment and required a washout period. This typically occurred between one and two months before randomization.

No patients were allowed to continue on anti-TNF therapy during the study but they could receive stable doses of DMARDs or anakinra during the trial. There were two sequential co-primary

outcomes, the first the ACR 20 at six months and the second improvement in physical function.

(Slide.)

Due to the novel nature of the patient population, we took rigorous measures to ensure that the desired patient population was captured in the study. Only patients with lack of efficacy on anti-TNF therapy were eligible. Patients were required to have a minimum of 10 swollen and 12 tender joints with an elevated CRP despite at least three months of treatment with anti-TNF therapy.

Some patients has active RA directly observed by the investigator while on anti-TNF therapy. These patients were designated as recent users and these are the patients who required a washout one to two months before the study start.

Other patients had discontinued anti-TNF therapy in the past due to lack of efficacy. These patients were designated as prior users and, as source documentation of their disease history was required, typically this was in the form of a chart note or a referral letter. These documents were

monitored by study personnel. Randomization was stratified on the basis of whether a patient was a recent or a prior user.

The typical patient in the study was about 50 years old, female, Caucasian and had long-standing RA, on average, 11 to 12 years.

(Slide.)

About 40 percent of patients in both treatment groups were recent users of anti-TNF therapy. Between 60 to 68 percent were infliximab users. Conversely, between 32 to 40 percent were etanercept users. Of the overall patient population, about 20 percent had tried both therapies.

The protocol specified a minimum 3-month trial be given before a patient was considered to an inadequate responder. In actuality, the median duration of dosing was about eighth months which indicated that patients had been given an adequate therapeutic trial before they were considered to be inadequate responders.

(Slide.)

In this trial, patients in both groups had highly active RA at baseline, again as evidenced by their tender and swollen joint counts, HAQ disability scores, CRP values and DAS 28 scores. The efficacy outcomes in this trial were similar to those in methotrexate-inadequate responders.

(Slide.)

86 percent of patients in the abatacept group completed the 6-month double-blind period. There were fewer discontinuations overall in the abatacept group, 14 percent versus 26 percent. The rate of discontinuations due to adverse events was comparable and the major difference between the groups was in the rate of discontinuation due to lack of efficacy, 5 percent versus 20 percent, respectively.

(Slide.)

Abatacept was significantly more effective in inducing an ACR 20 response. Statistically significant efficacy was observed by Day 15 and was sustained at all subsequent study visits. About 50 percent of patients treated with abatacept had an

ACR 20 response and six months.

(Slide.)

The left figure shows that the ACR 70 response rate for abatacept-treated patients was significantly greater than for placebo-treated patients. Significance was observed after two months of therapy, Day 57, and was sustained for the six-month double-blind period.

About 10 percent of patients on abatacept achieved an ACR 70 response at six months. The right panel shows that a greater proportion of patients on abatacept either had no tender or swollen joints after six months of therapy.

(Slide.)

Subgroup analyses from this study are presented using the same format as shown previously. The treatment effect for abatacept was consistent across multiple subgroups including age, gender and body weight. In addition, we did two other analyses which were of particular clinical relevance in this study. They were the history of anti-TNF use and the type of anti-TNF used.

Abatacept was consistently efficacious regardless of whether the patient was a recent or prior user of anti-TNF therapy. It was also effective regardless of whether the patient had had an inadequate response to etanercept, infliximab or to both therapies.

(Slide.)

Abatacept-treated patients were also significantly more likely to have improvement in physical function.

(Slide.)

Quality of life also significantly improved in this patient population despite the chronicity and activity of their disease at baseline. Patients treated with abatacept had significantly greater improvements in both the physical and the mental component scores of the SF-36.

(Slide.)

Abatacept was significantly more effective than placebo in improving each of the eight dimensions of quality of life in the SF-36. The

treatment effect for abatacept was consistent across all eight domains.

(Slide.)

At the beginning of this presentation, we proposed that abatacept, by virtue of its mechanism of action, would decrease the production of pro-inflammatory cytokines, matrix metalloproteinases and autoantibodies. Do the clinical data support this hypothesis?

(Slide.)

We compared systemic levels of biomarkers at baseline and at six months in each of the three key efficacy trials. Selective data representative of all three trials are shown from the phase III pivotal trial in anti-TNF-inadequate responders. Consistent with the central role of T-cell activation in the pathogenesis of RA, we observed reductions in the levels of the pro-inflammatory cytokines TNF-alpha and Il 6, the proteolytic enzyme matrix metalloproteinase 3, or stromolycin, and the autoantibody rheumatoid factor.

8 percent of patients treated with

abatacept who were initially positive for rheumatoid factor had undetectable rheumatoid factor at six months versus 0 percent of placebo-treated patients. Collectively, these data support the hypothesis that abatacept, by inhibiting T-cell activation, decreases the production of effector molecules that, together, mediate joint inflammation and structural damage in patients with RA.

(Slide.)

In conclusion, abatacept demonstrated consistent efficacy in patients with active RA despite existing therapies. Abatacept demonstrated significant efficacy in inducing an ACR 20, ACR 50 and ACR 70 response and, in combination with methotrexate, abatacept inhibited the progression of structural damage.

This was consistent for both the progression of erosive disease and well as joint-space narrowing. In conjunction with the ACR 20 data, the results demonstrate that abatacept is an efficacious disease-modifying therapy for the

treatment of patients with active RA.

Patients treated with abatacept also had meaningful improvements in both physical function and quality of life. Phase II data demonstrated that these improvements were sustained over at least two years.

Finally, treatment with abatacept led to major reductions in disease activity in both patient populations, despite the activity and chronicity of their disease. We observed meaningful improvements in ACR 70 response rates, major clinical responses and in a proportion of patients with no active joints after treatment.

Thank you for your attention.

(Slide.)

Dr. Dan MacNeil, our lead physician from the Pharmacovigilance Team, will now review the safety of abatacept.

Dan?

Safety Presentation

DR. MacNEIL: Thank you, Dr. Vratsanos. Good morning.

(Slide.)

The safety presentation begins with an overview of methods used to assess safety, a description of the patient population and a brief summary of the general safety and tolerability findings. It then proceeds to a detailed discussion of safety topics relevant for immunomodulatory therapy, infection and malignancy, and concludes with a discussion of our pharmacovigilance plan.

(Slide.)

Our presentation is based on safety data provided to and reviewed by the FDA in the BLA and in the four-month safety update. The presentation includes adverse events occurring up to 56 days following the last dose of study medication. 56 days is approximately half-lives of the drug in the peripheral blood.

Adverse events were classified into terms and categories using a standard coding dictionary, MedDRA or Medical Dictionary for Regulatory Activities. The investigators determined whether

adverse events were serious based on accepted regulatory criteria and whether they were of mild, moderate, severe or very severe intensity based on a predefined scale of functional impairment.

(Slide.)

Data from five clinical trials make up our core safety database. Each of these trials included a double-blind portion of at least six-months in duration followed by an open-label extension. The aggregation of data from our double-blind portion of these studies resulted in an experience with 1955 patients exposed to abatacept and 989 patients exposed to placebo.

After the blinded portion of the trials, 2339 patients continued on into open-label extensions. Our cumulative experience expressed as the number of patients who received at least one dose of study drug in either double-blind or open-label includes 2688 persons exposed to abatacept in the intended RA population.

(Slide.)

In double-blind, the total exposure was

1688 person years and the median exposure to abatacept was 12 months. In our cumulative double-blind and open-label experience, the total exposure was 3826 person years, more than twice the exposure in double-blind alone. The median exposure was 20 months.

Approximately 1500 patients were exposed for at least one-and-a-half years and approximately 150 were exposed for at least three years.

(Slide.)

Patient characteristics were comparable across treatment groups. The mean age was in the early 50s. Most patients were female and most were Caucasian. The mean disease duration was ten years. A high proportion of the population was receiving concomitant treatment with methotrexate and systemic steroids. A small number of patients received concomitant biologic therapies.

(Slide.)

Overall, there is an approximately 4 percent increase in reports of adverse events with abatacept as compared to placebo. As seen in the

middle rows, serious adverse events and discontinuations due to adverse events were about 1.5 percent more frequent without abatacept than with placebo. Deaths were infrequent and comparable across treatment groups.

(Slide.)

The greatest difference between treatment groups was in the frequency of headache which occurred in 18.2 percent of abatacept and 12.6 percent of placebo-treated patients. Other events which were reported at least 2 percent more commonly with abatacept than with placebo were nasal pharyngitis, dizziness, hypertension and dyspepsia. These events were rarely reported as serious events and rarely required discontinuation of therapy.

(Slide.)

Overall, serious adverse events were reported in 1.3 percent more abatacept than placebo-treated patients. The most common class of serious adverse events was musculoskeletal and connective-tissue disorders. These events were

generally manifestations of rheumatoid arthritis or procedure performed for its treatment such as joint replacement.

The greatest difference between groups, 1.1 percent, was in infections and infestations. Events occurred in 3 percent of abatacept and 1.9 percent of placebo-treated patients. This was the only case in which a difference of 1 percent or more was observed between treatment groups. A smaller difference between treatment groups, 0.8 percent, was observed in the injury, poisoning and procedural complications class. These were falls and fractures which were unlikely related to abatacept.

Neoplasms, including benign and malignant lesions, were reported in 1.4 percent of abatacept and 1.1 percent of placebo-treated patients.

(Slide.)

The proportion of deaths was comparable across treatment groups. The distribution of the causes of death was also similar.

(Slide.)

Our development program included 338 patients treated with abatacept or placebo in combination with marketed biologic RA therapy. From a safety standpoint, this subpopulation was of interest because historical experience has suggested an increased risk of infection with biologic therapies when biologic therapies for RA are used in conjunction with one another.

(Slide.)

The risk of serious infection appeared to be increased in patients treated with abatacept in combination with biologic background RA therapy. Although the number of patients with serious infections is quite small, only 11, these patients fall mainly in the abatacept group yielding a rate of serious infections that is roughly three times higher with abatacept than with placebo.

The number of patients with malignancies, only three with non-melanoma skin cancers, is too small to interpret. Overall, these data suggest an added risk of infection when abatacept is used in conjunction with another biologic agent. This

added risk would need to be offset by substantial efficacy in order to recommend the use of abatacept in this setting.

As described in the briefing document, the limited data available in this population does not demonstrate robust or consistent efficacy. Therefore, our proposed product label warns against the use of abatacept in combination with another biologic RA therapy.

(Slide.)

This portion of the presentation includes a detailed assessment of infections and malignancies. Infections were evaluated from the following perspectives: first, their frequency and type; next, their severity based on the investigator's determination of seriousness and intensity, the use of intravenous antibiotics, the frequency of discontinuation of study drug and the frequency of death; then, the incidence over time during the cumulative double-blind and open-label experience; finally, the clinical characteristics of three types of infections of particular

interest; pneumonia, herpes and tuberculosis. The assessment of the risk of infection is based on the totality of data provided by these evaluations.

(Slide.)

Overall, infections were reported in 53.8 percent of patients in the abatacept group compared to 48.3 percent of patients in the placebo group. The most common types of infections in both treatment groups involved the respiratory and urinary tracts. Nasal pharyngitis was the only type of infection reported 2 percent more commonly with abatacept than with placebo.

(Slide.)

Serious infectious adverse events occurred in 3 percent of abatacept in 1.9 percent of placebo-treated patients, a difference of 1.1 percent. The most common types of serious infections in both treatment groups were pneumonia and cellulitis. Both occurred with comparable frequency across treatment groups. No other type of serious infection was reported in more than 0.2 percent of abatacept-treated patients.

(Slide.)

The majority of infectious adverse events were rated by the investigator as mild to moderate in intensity. In both treatment groups, between 2 and 3 percent of patients experienced a severe event and less than 1 percent experienced a very severe event.

(Slide.)

Another indicator of severity is the use of intravenous antibiotics. In the phase III trials, the rate of intravenous antibiotic use was comparable in abatacept and placebo-treated patients. About 1 percent of patients in both treatment groups discontinued therapy for an infectious adverse event. The specific infections resulting in discontinuation were similar across treatment groups.

(Slide.)

Three patients had infections resulting in death. One abatacept-treated patient died from bronchopulmonary aspergillosis. One placebo-treated patient died from Pneumocystis

infection and one from sepsis.

(Slide.)

The rate of serious infections does not appear to increase over time. The upper row of data shows the number of events and person years of exposure at six-month intervals. There are approximately 3100 patient years of exposure up to Month 18 and 700 patient years of exposure beyond Month 18.

Highlighted in the middle are the incidence rates of serious infections per 100 person years within each six-month exposure window with the corresponding 95 percent confidence intervals below. The incidence rates per 100 person years range from 3.92 to 1.53. There appear to be no trends in the rates over time.

Three types of infections were considered to be of particular interest; pneumonia, herpes and tuberculosis.

(Slide.)

Pneumonia was evaluated as a common and often serious infection which is frequently

bacterial in origin. For this assessment, both serious and non-serious events were evaluated and the range of dictionary terms consistent with pneumonia was included. The overall frequency of pneumonia was higher with abatacept than with placebo, 2.1 versus 1 percent, and the time-to-onset somewhat shorter.

The duration of the events was similar across treatment groups at 12 to 14 days. The number reported as serious, severe or very severe was comparably across treatment groups and the number resulting in discontinuation was low. Overall, while pneumonia occurred more commonly with abatacept than with placebo, it appeared to be similar in its clinical characteristics.

(Slide.)

A second type of infection, evaluated in detail, was the herpes family of infections. Herpes infections are of particular interest because of the role played by T-cells in their suppression. Herpes simplex was reported in about 1 percent more abatacept than placebo-treated

patients. No cases of herpes simplex were reported as serious or resulted in discontinuation of therapy.

Herpes zoster was reported in similar proportions of patients across treatment groups. One case of zoster was reported as serious and one case resulted in discontinuation of therapy. There were three reports of varicella in abatacept-treated patients. None were reported as serious. All were reported as moderate in intensity and all resolved appropriately. There were no reports of Epstein-Barr virus or cytomegalovirus.

Overall, the data suggest that risk of herpes infections, especially herpes simplex, may be increased with abatacept. However, serious herpetic infections or herpetic infections requiring discontinuation of abatacept were infrequent.

(Slide.)

The third type of infection evaluated in detail was tuberculosis which has been reported

with increased frequency with currently marketed biologic RA therapies. Because of this experience, screening procedures were implemented in our trial program to exclude patients with latent or incompletely treated tuberculosis.

There were two cases of presumed t.b. with abatacept in the cumulative experience. Neither was confirmed by culture or acid-fast stain and neither had a typical presentation for tuberculosis.

The first patient had an enlarged cervical lymph node which was excised. After a delay of approximately eight months, the histology was noted to contain granulomata consistent with t.b. The patient remained asymptomatic on abatacept throughout this time.

The second patient had constitutional symptoms and bibasalar infiltrates on chest X-ray. Anti-tuberculous therapy was initiated empirically after a failure to respond to antibiotics. Bronchoalveolar lavage and transbronchial biopsy were negative.

A third case was reported in a placebo-treated patient during double-blind.

(Slide.)

Based on the data present, we conclude that abatacept treatment is associated with a small increase in the frequency of infections including serious infections. The type, severity, treatment, duration and outcome of the infections which occurred on abatacept were qualitatively similar to those occurring on placebo. The outcomes were also favorable.

(Slide.)

Several factors warrant a close evaluation of the risk of malignancy with abatacept. Immunosuppressant therapies have been associated with an increased risk of malignancy especially lymphoma and squamous-cell carcinoma of the skin. In addition, RA, itself, is believed to be associated with an increased risk of lymphoma.

Our discussion of malignancy will begin with the non-clinical findings for abatacept. The overall clinical experience will then be reviewed

in detail before concluding with the discussion of two specific malignancies, lung cancer and lymphoma, which were the most commonly observed solid and hematologic malignancies in the abatacept clinical program.

The assessment of malignancy, which concludes this section, will focus on the following considerations; frequency relative to placebo during double-blind, incidence over time during the cumulative double-blind and open-label experience, incidence relative to reference populations including the U.S. general population and RA-specific cohorts, clinical features, including risk factors, histology, treatment and outcome.

The overall assessment of the risk of malignancy with abatacept is based on the totality of data provided by these evaluations.

(Slide.)

To determine the potential for abatacept to cause malignancies in humans, a panel of mutagenicity and clastogenicity studies was conducted. These demonstrated that abatacept is

not genotoxic. In addition, a long-term rodent carcinogenicity study was conducted. Such studies are generally not conducted with protein therapeutics because of lack of bioactivity in immunogenicity in rodents versus antibody response to itself.

In this study, mice were exposed to abatacept for up to 88 weeks at approximately 1 to 3-fold the human exposure. Sustained immunomodulation was achieved at all dose levels as demonstrated by lack of development of anti-abatacept antibodies.

An increase in the incidence of lymphomas was observed at all doses and mammary-gland tumors at the highest two doses in females. In both tumor types, viruses known to cause these murine tumors were detected. Murine leukemia virus was in the genome of mice from this study. Mouse mammary tumor virus was present in the mammary-gland tumors.

We concluded that the increase of malignancies were due to inhibition of the host

response to these viruses.

(Slide.)

Additional nonclinical information on the risk for virally associated malignancy in humans was provided by a one-year monkey toxicology study. This was a convention toxicology study that was enhanced to evaluate lymphoid neoplasia. Our other immunosuppressive agents have been demonstrated to induce neoplastic and pre-neoplastic changes in this species within this time frame.

In this study, there was no evidence of any malignancies or pre-neoplastic lesions such as lymphoid hyperplasia following one year of treatment with abatacept at exposure multiples up to 9-fold the human exposure. Lymphocrypto virus, which is known to induce lymphoma or pre-neoplastic changes in immunosuppressed monkeys, was present in the genome in 38 of the 40 monkeys studied.

Overall, the results of the murine study suggest that abatacept has the potential to increase the risk of virally associated malignancies in humans. While the results of the

non-human primate study partially temper this concern, the relevance of these findings is best addressed in the human clinical experience.

(Slide.)

Overall, 1.3 percent of abatacept-treated patients reported a malignancy as compared to 1.1 percent of placebo-treated patients. Non-melanoma skin cancers were the most frequently reported malignancies occurring in 0.8 percent of abatacept-treated and 0.6 percent of placebo-treated patients.

Solid-organ cancers were next most frequent occurring in 0.5 percent of patients in each treatment group. Hematologic malignancies occurred in two abatacept-treated and no placebo-treated patients.

Turning to the individual malignancies, among the non-melanoma skin cancers, basal-cell cancer was about twice as common as squamous-cell carcinoma in both treatment groups. Among the solid tumors, there were eight types reported. The most common was lung which was reported in four

abatacept versus zero placebo-treated patients. Breast, prostate and colorectal cancer which, together with lung cancer, represent the four most common tumor types in the U.S. general population, were infrequent.

Breast cancer occurred in one abatacept and two placebo-treated patients, prostate cancer in one abatacept-treated patient and colorectal cancer in no patients. Thyroid cancer occurred in two patients. Among patients with hematologic malignancies, there was one lymphoma and one myelodysplastic syndrome in the abatacept group.

To understand the risk of malignancy with increased duration of exposure, we examined the incidence of malignancy in our cumulative, double-blind and open-label experience.

(Slide.)

The center column of this table displays the incidence rate of malignancies per 100 person years for the double-blind period. The right-hand column displays the rates for the combined double-blind and open-label period. Highlighted in

yellow are the rates for the subgroups of nonmelanoma skin cancer, solid-organ cancer and hematologic. In the subgroups, the rates have not increased with increased duration of exposure.

Turning to the individual tumor types, there have been four additional reports of lung cancer since the double-blind period. The incidence rate, however, is unchanged. The incidence rates of breast and prostate cancer are unchanged and there are no reports of colorectal cancer.

There have been three additional reports of lymphoma. The incidence rate is now 0.10 per 100 person years versus 0.06 in double-blind. Other individual cancers remain infrequent.

It should be noted that potentially virally mediated tumors were infrequent. Lymphoma occurred in four patients and cervical cancer in one. It has not been possible to determine the EBV or HPB status of these patients. Other tumors related to viral infection, including hepatocellular carcinoma, head and neck cancer and

Kaposi's sarcoma were not observed.

(Slide.)

The overall incidence of malignancies in the clinical program was compared to the U.S. general population using the surveillance epidemiology and end-results cancer statistics, SEER, database, adjusted for age and gender. The overall rate of malignancy with abatacept was similar to the U.S. general population.

Certain malignancies, such as lymphoma and lung cancer, were seen more frequently than in the U.S. general population while other malignancies, such as colorectal and breast, were decreased in incidence.

(Slide.)

To put the observed pattern of malignancies with abatacept in context, we looked in the literature at studies which compared the incidence rates for malignancies in RA patients to those in several general populations. Presented here are the estimated standard incidence ratios from these studies for lymphoma, lung, colorectal

and breast malignancies.

The pattern of comparative SIRs is consistent with that observed in the abatacept clinical program. The published reports have consistently described and increased incidence of lung cancer and lymphoma and, although less consistent, a decreased incidence of breast and colorectal cancer in RA patients.

(Slide.)

We also compared the rates in the development program where all patients were treated with nonbiologic DMARDs to the rates in DMARD-treated patients in several established RA cohorts. These were the British Columbia RA registry in Canada, National Databank for Rheumatic Diseases in the United States, and the Norfolk Arthritis Registry from the U.K.

(Slide.)

The results of this analysis are consistent with the results just described. In particular, for lymphoma, 1.1 cases would have been expected based on the U.S. general population

incidence rate. Based on the RA DMARD cohorts, 2.4 to 3.1 lymphomas would have been expected, more than the general-population incidence rates would predict and consistent with published reports.

The number of cases observed in the abatacept studies, four depicted at the top, is consistent with what would be expected based on the published literature and these RA cohorts.

(Slide.)

For lung cancer, four cases would have been predicted based on the U.S. general population incidence rate. Based on the RA DMARD cohorts, 3.6 to 9.9 lung cancers would have been expected. The range is consistent with published reports describing an increased incidence of lung cancer in RA.

The number of cases observed in the abatacept studies, eight, is consistent with what would be expected based on the published literature and the range of estimates from these RA cohorts.

(Slide.)

I will now turn to a more detailed

examination of lung cancer and lymphoma. The clinical features of the four reported lymphomas are summarized here. All four were of the non-Hodgkins type. Three were B-cell lymphomas. The fourth was of T-cell lineage.

These cases developed at various lengths of time on treatment with abatacept ranging from 203 to 1086 days. One lymphoma developed in the thyroid gland in the setting of Hashimoto's thyroiditis, a known risk factor for lymphoma.

Two occurred in patients who had been treated with infliximab and one occurred in a patient who was receiving concomitant etanercept. The history of treatment with TNF-blocking agents suggests that these patients had severe RA.

Overall, these cases had a typical presentation for lymphoma associated with RA. The histologic types were typical. They occurred in patients whose risk of lymphoma may have been elevated by the severity of their RA by their prior immunosuppressive exposure and, in one patient, by concurrent Hashimoto's thyroiditis.

They occurred at varying points in the course of therapy with abatacept. There was no cluster of events early in the treatment course nor was there an increase in frequency with increasing duration of exposure. There were, thus, no unexpected features that would raise concern that abatacept contributed to their development.

(Slide.)

The second malignancy we examined in detail was lung cancer. The eight cases of lung cancer all occurred in middle-aged to elderly patients. Seven of the eight were smokers. The tumors had a variety of histologic types including adenocarcinoma, squamous-cell carcinoma, small-cell and carcinoid. There was no predominant cell type.

The time to onset varied from 29 days to 484 days with on cases reported beyond the first 18 months of therapy. In two cases, the duration of treatment prior to diagnosis was short, at 29 and 100 days. An independent review of diagnostic, pathologic and radiographic findings was undertaken for all lung malignancies. For two of the cases of

lung cancer, this review indicted pre-existing abnormalities suggestive of malignancy. These two cases were distinct from the two cases just mentioned with a short duration of treatment prior to diagnosis.

Overall, these cases had a typical clinical presentation with no clinical features that would raise concern that abatacept had contributed to their development. Moreover, based on the very short treatment period prior to diagnosis and on independent radiograph review, four of the tumors were likely to have been present prior to treatment with abatacept.

(Slide.)

In examining the incidence rate of lung cancer over time at six-month intervals, the incidence does not appear to increase with an increasing duration of exposure to abatacept. Although the bulk of exposure to study drug occurred during the first 18 months of treatment, there are, in aggregate, approximately 700 person years of exposure beyond 18 months with no

additional cases.

(Slide.)

Our safety presentation to this point had been based on data submitted to and reviewed by the FDA. We have recently analyzed data up to June, 2005 on patients continuing on into the open-label long-term study periods. Although not formally submitted to the FDA, we are presenting these malignancy data with their agreement.

(Slide.)

The overall exposure is now approximately 4800 patient years. As indicated in the center and right-hand columns of this table, the incidence of malignancy, by major category, skin, solid and hematologic, highlighted in yellow, remains similar to that described in the database submitted to the FDA and described earlier.

Although there have been three additional reports of lung cancer, the incidence of lung cancer remains stable at 0.23 per 100 person years and still in keeping with the RA cohorts. There have been no new reports of lymphoma.

Earlier, we showed you the incidence of lung cancer and lymphoma by duration of exposure. Those analyses were limited by the relatively small amount of exposure beyond 18 months of treatment, only 700 person years. With these new data, there are approximately 1400 person years of exposure beyond the 18-month point. With this additional data, there continues to be no evidence of an increase in the risk of malignancy with additional duration of treatment.

Overall, the frequency of malignancies was similar to placebo in the blinded portion of the clinical trials. In comparison to the general population, overall malignancies were also similar and individual malignancies were higher or lower in a pattern consistent with an RA population.

Compared to the RA cohorts, the numbers of observed cases of lymphoma and lung cancer are also consistent with what would be expected. The totality of evidence, examined for both malignancies including their clinical presentation, histologic type, time to onset, risk factors and

for lung cancer, evidence of pre-existing disease does not suggest an increased risk with abatacept.

Virally mediated malignancies were a particular concern because of our nonclinical findings. Based on the current data, there is no suggestion of an increase in these malignancies.

(Slide.)

These results of our safety analysis do not indicate that abatacept increases the risk of malignancy beyond that which would be expected for the RA population. Nevertheless, the size of the clinical-trial population and the duration of exposure do not rule out a small increase in risk and do not address the long-term safety of abatacept in clinical practice.

Our pharmacovigilance plan is intended to provide a more definitive assessment of long-term risk.

(Slide.)

In addition to the standard pharmacovigilance assessment of individual and aggregate adverse-event reports, we will enhance

data collection for events of special interest by using special-event forms. We also will make telephone contact with event reporters to obtain prompt and consistent information on selected events.

We will extend our long-term open-label clinical trials for up to five years to systematically collect safety information. These studies will include 1000 to 2000 patients. Because women of child-bearing potential will be receiving abatacept, we will participate in a voluntary registry to monitor reports of pregnancy and its outcome.

We also plan to conduct two large observational safety studies.

(Slide.)

The studies are designed to provide complementary information on abatacept use and its safety in the postmarketing period to support ongoing benefit-risk assessment. Selected adverse events of interest include malignancy and infection. The studies will estimate incidence

rates overall and in subgroups. They will compare abatacept incidence rates to other therapies.

The studies will also allow a description of patterns of use and will accrue information useful to investigate unanticipated adverse events.

(Slide.)

The insurance claims database study will describe that short-term incidence of targeted events which will be confirmed by chart review. It will use the data of the UnitedHealthcare Group, a combination of insurance plans with open formulary which includes 20 percent of U.S. prescriptions and biologics administrations.

It is anticipated that the database will include 1200 new starts of abatacept patients matched to patients on comparator drugs within the first three years. It will be able to detect an approximate doubling in risk of uncommon events such as hospitalization with pneumonia.

(Slide.)

The prospective cohort study will describe both the short-term and long-term incidence of

adverse events. The study will be conducted using an existing independent registry enrolled through physicians. It will include 5000 patients initiating abatacept and approximately 15,000 adding or initiating comparator treatment with DMARDs or biologics.

Follow up will be for five years after the last patient has enrolled. The study will assess both short- and long-term incidence of selected adverse events and can potentially assess benefit by such measures as health assessment questionnaire and the pain score.

The relative risks and confidence intervals for abatacept compared to other DMARDs and to biologics will be estimated separately. The study will be able to detect an approximate doubling of rare events such as lymphoma and lung cancer compared to patients initiating DMARDs.

(Slide.)

The totality of data in the clinical development program demonstrates that abatacept is generally safe and well tolerated. The primary

identified risk is infection with a small increase in serious infections of 1.0 percent. However, the type, duration, treatment and outcome are similar to placebo.

The malignancy risk overall is similar to placebo and consistent with the RA population. But the current assessment is not definitive. Our pharmacovigilance plan includes two large observational studies which will better define long-term risk and the risk of rare events including lymphoma, other malignancies and serious infections.

Thank you for your attention. Let me now introduce Dr. Brian Daniels who will conclude today's presentation.

DR. GIBOFSKY: Dr. Daniels, the presentation is approximately ten minutes overtime. I would ask you to keep your closing comments rather short.

Closing Comments

DR. DANIELS: What you have heard today represents the results of over ten years of

research and development and the treatment of over 2600 patients with abatacept. In our assessment, through its unique mechanism of action, abatacept provides an important new therapy for patients and physicians in the treatment of rheumatoid arthritis.

RA is a diverse disease with incompletely understood pathogenesis. Therefore, treatment requires a variety of therapy options. No single therapy works for all patients and all therapies carry some risk. Rheumatologists need to switch and combine therapies, balancing benefits and risks, to treat their patients.

Abatacept provides a new option which may be used in combination with methotrexate or other disease-modifying agents. In order to realize these benefits, it must be used appropriately, though, and its potential risks must be fully identified. Our current recommendations for its appropriate use based on its risk are straightforward.

We recommend that physicians should employ

routine screening using standard guidelines for latent infections and malignancies. We recommend that physicians and patients be alert for signs and symptoms of infections during therapy and we have also identified a higher risk of infection in combination use with biological agents and recommend against such use.

These and other recommendations will be emphasized in physician and patient-education programs. As with all our new products, Bristol-Myers Squibb will not conduct direct-to-consumer advertising on abatacept for at least one year following its approval. This will ensure that the prescribing rheumatologist first understands its appropriate use.

Now, to continue to understand abatacept's potential risk, Bristol-Myers Squibb has submitted to the FDA an extensive postmarketing pharmacovigilance plan which Dan described to you today. This program will allow for continuous benefit and risk assessment through multiple data sources and will advance the overall scientific

knowledge of the disease and its treatment options.

We look forward to have the opportunity to answer any questions you may have about abatacept and its development. I will turn the podium over to Dr. Waclawski for any questions.

DR. GIBOFSKY: Thank you.

Questions from the Committee

DR. GIBOFSKY: Are there questions from the panel? Dr. Elashoff?

DR. ELASHOFF: I have three questions. The first is on Slide 53 which has to do with the biomarkers. I didn't notice anything about standard errors or significance in those comparisons.

DR. WACLAWSKI: Dr. Vratsanos?

DR. VRATSANOS: There was a significant degree of inter-patient variability. However, we did not perform formal statistical testing on these analyses.

DR. ELASHOFF: So I would take it that probably means they are not significant. Okay. Next question has to do with something that--it

seems to me, in the old days, that we insisted on studies being done only in U.S. populations or at least one such study.

As near as I could tell, all of these studies were done on a mix of U.S. and other country populations. So one question is addressed to the FDA later, have those guidelines changed. A second question to you, have you broken out efficacy and safety issues by country of where the studies were done.

DR. WACLAWSKI: Dr. Vratsanos?

DR. VRATSANOS: I can address the efficacy issues from the two phase III pivotal trials. The first I will review is the phase III trial in methotrexate-inadequate responders.

May I have Slide 43b-20, please.

(Slide.)

This shows the ACR 20 response rate at six months, the primary endpoint in the four geographic regions where the study was conducted. The majority of patients, 95 percent, came from North America, South America or Europe.

What we see here is that the placebo response was variable in different geographic regions. However, importantly, the treatment effect for abatacept was consistent at 30 percent in each of the major geographic regions where the study was conducted.

I would like to review also the data from our trial in anti-TNF-inadequate responders. This study was conducted in North America, predominantly the United States and Canada and in Europe.

May I have Slide 44b-19, please.

(Slide.)

We saw consistent efficacy in both regions.

DR. ELASHOFF: My last question has to do with the large observational studies you are planning. According to my reading, the efficacy studies were all powered at 90 percent to detect a 20 to 25 percent difference in ACR 20. Also, according to my reading, the safety studies which you saw are designed to detect relative risks greater than are both powered at 80 percent; is

that correct?

DR. WACLAWSKI: I will have to ask our lead epidemiologist, Dr. Skovron, to respond to your comment.

DR. SKOVRON: Good morning. Yes; the observational studies are powered to detect a doubling in risk with a power of approximately 80 percent.

DR. ELASHOFF: In other words, the studies were designed with a lot bigger power to detect efficacy than you are planning to use in detecting safety.

DR. GIBOFSKY: Is that a question, Dr. Elashoff?

DR. ELASHOFF: It is a statement.

DR. GIBOFSKY: Dr. Finley.

DR. FINLEY: I have two questions for Dr. MacNeil just to better characterize the patients. I am referring to Slide 60. Just wondered the percentages, as far as female, were about 80 percent. I was wondering, of those with the mean age being 53, what were the number, if you knew, of

those who were thought to be of childbearing age.

DR. WACLAWSKI: I am not sure that we have the demographics broken down in that level of detail. I will look to the team. Dr. Natarajan, do we have that information with us?

DR. NATARAJAN: We can get it.

DR. FINLEY: Then the second question, given the review of the safety on lung carcinomas and it was characterized about the number who were identified as having cancer and the number that were smokers, what was the number that were smokers in the overall population, again looking at Slide 60? Did you know that data?

DR. WACLAWSKI: Our case-report forms collected smoking status as a check box where there was a yes or no question for tobacco use. When we looking into that, we found that patients checked tobacco use "yes" in about 20 to 25 percent of the time across the population.

DR. FINLEY: Thank you.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I have three questions for

you. One is what was striking about the very comprehensive presentation of clinical trials--to me, one of the things that was striking, was the young age of the subjects. 52 isn't especially young, although, as I get older, it seems young to me.

But most studies are now showing that rheumatoid arthritis patients, on average, are much older than this. I am wondering if you had an upper age cutoff and, while your efficacy looked really good in older people--in fact, it looked slightly better--I would be real concerned about adverse events in older people.

I wondered if you had data on adverse-event rates comparing placebo and active therapy in people over age 60 railroad over age 65. So, a couple of questions, then. One is, was there an upper age cutoff for these studies? Why did you recruit people who were relatively young? Even in RA trials, now, the average is about 59 or 60. So this is really a young population.

Then were there differences in adverse

events in this older age group?

DR. WACLAWSKI: I would like to have Dr. MacNeil first comment with respect to the safety profile that we observed in elderly patients and then have Dr. Natarajan help me with the response to the age distribution of the patients, particularly the cutoff. I believe we cut the clinical-trial experience off at the upper age around 72.

DR. FELSON: So you didn't allow--so people over age 72 were not eligible for this study.

DR. WACLAWSKI: Let me confirm that while Dr. MacNeil answers your other concern which is what is our safety experience in patients who are, in our definition, elderly, over 65 years of age?

DR. MacNEIL: In the over-65 population, what we noted as a particular difference was in reports of serious adverse events, predominantly those that were malignancies and infections. The types of infections that the elderly experienced were similar to those that the total population

experienced and their outcome was also similar. They were predominantly bacterial and then involved the respiratory tract and also soft-tissue type infections.

The malignancies were scattered with the exception that the four cases of lung cancer that occurred in the double-blind experience were in patients over the age of 65. We recognize that elderly patients have this increased risk of serious adverse events and there will be a precaution for the use of the drug in the elderly in our label with a risk/benefit assessment being on the part of the physician and the patient that there is established efficacy in this patient population over the age of 65.

DR. FELSON: Dr. MacNeil, just a short follow up. I am unclear, based on what you said--so the overall adverse-event rate was increased in older people. Was the comparative adverse-event rate in active therapy versus placebo different in older people?

DR. MacNEIL: May I have Slide 65B-3,

please.

(Slide.)

This is the experience in the over-65 age group. As I noted, serious adverse events--there was a greater difference in serious adverse events in the over-65 group with serious infections being 5.6 versus 2.7 percent and also malignancies 5.3 versus 2.7 percent.

DR. GIBOFSKY: Anything further, Dr. Felson?

DR. FELSON: Well, I guess I would like to hear about the age cutoff issue and why you decided on an age cutoff. Just as a comment, there has been literature, general medical literature, advocating that people of all ages be included in trials, just like pediatric efficacy. I think that there is concern that we are using these drugs a lot in elderly people without knowing a lot about their efficacy and safety.

DR. NATARAJAN: I just want to assure you that there was no age cutoff. There was an error, actually. There was no age cutoff. The ages

ranged between 17 to 87 years in our studies.

DR. WACLAWSKI: If I could, perhaps, have Dr. Vratsanos, also, add to the point about the efficacy in the elderly because I don't think that we have represented that, which is part of our decision that, in use in elderly is counterbalanced by an indication of efficacy in that subgroup. I would like to have Dr. Vratsanos go ahead and show us that efficacy data as well.

DR. VRATSANOS: May I have Slide 65b-2, please.

(Slide.)

We saw consistent efficacy in the elderly on both pivotal trials. What is shown here are the ACR 20 response rates for the primary endpoints in each trial, six months for the methotrexate trial, six months for the anti-TNF trial. Patients greater than 65 years old had consistent reduction of signs and symptoms along with the rest of the population.

DR. FELSON: I have a couple of other small questions that are different from this. One

is, you commented, I think, that you would recommend against use with biologics. Does that include anakinra? Was anakinra in this list?

DR. WACLAWSKI: At the moment, our proposal being that most of the experience we have is with anti-TNFs is that it would be limited to combination use with anti-TNF therapies. This is something, though, that is still under discussion with FDA as we continue to evaluate and review that particular recommendation.

DR. FELSON: Have you looked at infection rates in subjects in these studies co-treated with anakinra? You allowed anakinra use; right?

DR. WACLAWSKI: It was a very small population of patients. It was--I will ask Dr. MacNeil--do you recall the numbers of patients with anakinra? We can come back to that, but it was a very small population. Most of this experience comes from our phase II study where we used abatacept in combination with etanercept. Of course, in the DAS 31 study, our large safety study, it did allow anakinra But relative to those

300 patients or so that had the combination biologic use, I know the vast majority were with combination TNF inhibitors and there was a small number with anakinra.

DR. FELSON: Just to end, a brief follow up from Dr. Elashoff's question earlier about the carrying out of trials outside of the United States. In the one pivotal trial you showed information about where there were very large numbers, the largest contingent was represented by South America. The response rates were enormous including 45 percent placebo response rates which is, even though ACR 20 sometimes has high placebo response rates, that is really an incredibly high placebo research rate.

What can we make of that? Does that mean that these data are not valid, that there are some issues with the performance sites in South America? Now, granted, you were seeing the same differential efficacy in the United States. You showed evidence of that.

But what do we make of these very, very

high placebo response rates in South America?

DR. WACLAWSKI: I think it would be difficult for me to speculate as to why there was a difference by region where I think we tried to make the point that the important thing was the difference between placebo and abatacept in those regions. I can reassure that the studies were conducted under GCP with appropriate monitoring, with appropriate investigators, with appropriate training and investigators meetings and so forth.

So we are confident that quality of the study from the standpoint of the assessment of the outcomes is there and that the efficacy relative to placebo is fairly clearly demonstrated.

DR. GIBOFSKY: Dr. Ilowite.

DR. ILOWITE: I have a few quick questions. Regarding the patients who developed varicella, do you know anything about their exposure, their prior immunization status or their history of a preceding varicella clinical episode that might have made them immune?

DR. WACLAWSKI: Dr. MacNeil?

DR. NATARAJAN: If I could have Slide 62c-6, please.

(Slide.)

These were the three persons who had varicella in our double-blind and open-label experience. As you can see, these people, two of the three, did have a previous history of varicella. One was treated with antivirals, one with antibiotics and one not at all. You can see the duration of time to the onset of those events.

They were all reported as nonserious adverse events and recovered without anything unusual in their clinical picture.

DR. ILOWITE: Another question. I share with some of the other members of the committee that the drug will be used in populations in whom it has not been adequately tested and also in ways that it hasn't been adequately been tested. So, the first question is, do you have any maybe data from the diaries of patients and how they were doing towards the end of the dosing period?

As I understand it, the half life is about

11 days and they are giving drug at monthly intervals. Did they get worse toward the end, right before their next dose?

DR. WACLAWSKI: All the assessments that we showed today are based at trough levels--that is, at the visit immediately preceding the next infusion. So they would reflect an assessment in a patient that would be under chronic therapy close to their lowest levels of drug.

DR. ILOWITE: How did they do compared to right after the dose? Do you have data on that or no?

DR. WACLAWSKI: I don't think we have data like that; no.

DR. ILOWITE: Then could you give us some idea of the status of testing in children with JRA, studies in children. How are those going?

DR. WACLAWSKI: We just completed enrollment in a study of JRA. It is an ongoing study. It is part of our post-authorization commitment for the product to continue to complete that study. But it is completely enrolled and we

are continuing to investigate JRA.

DR. GIBOFSKY: Dr. Porter

DR. PORTER: You made a brief foray into multiple sclerosis which, I think, you described as a null study but with some confusing results in which the low-dose group had a substantial number of lesions over that of placebo and your high group less than placebo.

Are you confident that this drug can be given to patients with multiple sclerosis given the fact that you really don't have much strong data here and are you going to plan to include this in your pharmacovigilance program?

DR. WACLAWSKI: I want to ask Dr. Elliott Levy who is the lead clinical person from our immunology team to review the MS experience and to verify for you what we learned from that trial. But, just to reassure you, we are not recommending the use of abatacept in patients with multiple sclerosis. We haven't studied it that way. We are not investigating it for that indication here today.

But I think it is important to-

DR. PORTER: So, in your label, you will recommend that it not be used for MS.

DR. WACLAWSKI: We don't have a specific recommendation as such except to say patients with histories of autoimmune diseases, those types of precautions would be, aside from RA, the ones that you would have to have some caution. So, no; there is not a specific recommendation with regard to MS because this trial, as you have said, on its face, is very difficult to draw a conclusion from.

DR. PORTER: You are quite right.

DR. WACLAWSKI: I would like to ask Dr. Levy who can reassure the committee of what we learned from that study and explain what the status is with that trial.

DR. LEVY: Thank you, Tony. I would just like to reiterate what Tony said. We have no intention to, in any way, encourage the use of the drug in patients with multiple sclerosis and, as part of our postmarketing commitment, we will have the ability to authorize the--to monitor the use of

the drugs through the Healthcare Claims database. So we will have the ability to see whether, in fact, physicians are using in patients with multiple sclerosis.

That said, I am happy to describe to you the results of the studies you mentioned. We conducted a single trial in multiple sclerosis. This was a phase II, dose-ranging, randomized, double-blind, placebo-controlled trial. It was intended to compare the efficacy of two doses of abatacept, 2 milligram per kilogram and 10 milligram per kilogram, to placebo in patients with relapsing, remitting multiple sclerosis.

The trial was--I think, as you have said, it really provided a null result, very difficult to interpret in terms of either benefit or harm for four reasons. First, the trial was terminated early because of--for a variety of reasons. Secondly, the number of patients who were studied was small. In fact, in the 10 milligram per kilogram dose arm where there were results were superior to placebo, we have only 16 patients with

enough follow up to evaluate for efficacy.

Third, there are significant imbalances in the duration of follow up across treatment groups with longer follow up in the placebo and 2 milligram per kilogram arms and shorter follow up in the high-dose arm and, lastly, significant imbalances in baseline prognostic characteristics across the groups

DR. PORTER: Clearly, the study doesn't help us much. I am reassured that you are planning to have a pharmacovigilance program that will pick up MS patients as they get this drug, which they eventually will, for sure.

DR. LEVY: Yes. We see one of the virtues of the program is that it will enable us to monitor the actual use of the drug and to determine if, in fact, it is being used in ways that are inconsistent with the product labeling

DR. PORTER: And the result thereof.

DR. LEVY: Yes.

DR. PORTER: Thank you very much.

DR. HOLERS: I have questions related to

the safety and development of unintended autoimmunity as well as questions regarding the actual level of immunosuppression that this drug induces in patients. I think this is one way to help us judge what the risk of infections and malignancies might be.

So, with regard to the intended development of other autoimmune diseases, could someone comment on Dr. Daniels' reply that there is data in which the drug has been given to a mother and pups are evaluated for the development of autoimmune disease?

DR. WACLAWSKI: Yes. Dr. Helen Haggerty is our lead toxicologist. She is responsible and conducted those studies.

Dr. Haggerty?

DR. HAGGERTY: Helen Haggerty from the Department of Drug Safety Evaluation at Bristol-Myers Squibb. In a complete battery of reproductive and developmental toxicity studies, abatacept demonstrated no findings in any of the traditional endpoints that are incorporated into

these types of studies at up to 11 or 29-fold or human exposure.

As abatacept is an immunomodulatory agent, we added a number of additional special endpoints into our study of pre- and post-natal development in rats so that we could assess the effects of abatacept on the developing immune system of pups from dams that were dosed with abatacept through gestation and lactation.

If I could have Slide 30b-2.

(Slide.)

This slide here lists the evaluations that were conducted. We examined, throughout multiple time points, the drug level as well as anti-drug antibodies. In addition, at postnatal Week 7 and 8, when the animals were adults, we assessed the effect on the T-dependent antibody response as well as serum and globulin levels, lymphoid organ weights and lymphocyte phenotypes include NK cells.

When the animals were much older, at 16 weeks of age, we assessed for the presence of autoimmunity by looking at the presence of

antinuclear antibodies, serum and globulin levels. We conducted a complete clinical pathology assessment as well as the histology of lymphoid organs and select organs that were prone to autoimmunity.

This was five different organs including the kidney, the thyroid, the stomach, the pancreas and ovaries and testes.

The next slide, please.

(Slide.)

What we observed was at three-fold the human exposure, we had no effect on any of the parameters that were evaluated in these animals at 11-fold the exposure.

Next slide, please.

(Slide.)

We observed two findings. We had a nine-fold increase in the mean T-cell-dependent antibody response--this was observed in females only--and inflammation of the thyroid in one female rat out of ten males and ten females evaluated at this dose level in this cohort. We observed no

effect on any of the other organs that were evaluated.

So, based on the weight of the data here, we conclude that the risk to the developing immune system of human progeny at clinically relevant exposures is low as the findings were limited to two findings in either one gender and/or one animal and at the highest dose that was evaluated.

DR. GIBOFSKY: Dr. Holers, will you yield to an interim question from Dr. Elashoff about this slide.

DR. HOLERS: Yes.

DR. ELASHOFF: I assume that when you say "no effect," it means no statistically significant effect rather than no slightly negative-looking effect.

DR. HAGGERTY: In addition to statistics, we also looked at biological relevance.

DR. ELASHOFF: And these are done in groups of ten?

DR. HAGGERTY: Ten males and ten females per group.

DR. HOLERS: Were there specific studies done in mice that are genetically prone to the development of Type 1 diabetes in which this is the major disease in which this effect has been seen that Dr. Williams was describing; i.e., that regulatory T-cells are inhibited from their development and Type 1 diabetes ensues in the NOD mouse?

DR. HAGGERTY: We did not specifically do that.

DR. HOLERS: What about data with regard to the development in your patients undergoing clinical trials of antinuclear antibodies, anti-thyroid antibodies? Is there any data on the development of Type 1 diabetes-related autoantibodies and is this part of the pharmacovigilance proposal?

DR. WACLAWSKI: Two parts. I would like to have Dr. MacNeil first provide the committee with an overview of what we know about the clinical events of autoimmunity and we can also comment on the ANA antibodies in those other biomarkers.

Dr. MacNeil? While he is coming, the pharmacovigilance program is a large program. It is not only going to be able to helps us assess the long-term risks of infections and malignancies but other unexpected events can also be potentially detectable in an experience of that size.

One other point, because we have a couple of questions about pregnancy, I want to reinforce that our recommendation for labeling is a Pregnancy Category B which is we don't have good controlled clinical data in women so the drug should only be used if it is clinically needed. If the benefit-risk profile in the view of the physician is favorable, it may be used. But that is similar labeling to what has been also applied for the TNF inhibitors, other biologic therapies in this area. So I wanted to make sure the committee was aware of that. And Dr. MacNeil for the autoimmune spectrum of clinical events.

DR. MacNEIL: Let me first speak to the question of the seroconversion from a negative to a positive study.

If I could have Slide 64a-5 please.

(Slide.)

This is the data for the number of subjects who converted from a baseline negative to a positive ANA and also a double-stranded DNA. You can note that fewer patients actually converted on abatacept as compared to placebo at either the 6 or the 12-month period.

Turning to the autoimmune disorders, overall, there was a 2.9 versus 1.8 percent difference, abatacept versus placebo, in autoimmune disorders. Approximately 50 percent of those were keratoconjunctivitis sicca. The next most common were reports of psoriasis followed by vasculitis.

There was a single report of lupus in a person who was diagnosed on Day 8 in the trial. That person, in retrospect, had findings at baseline consistent with that. There was also a lupus-like syndrome in a person who was on therapy for approximately six months. That person was on concomitant adalimumab and the person stayed in the trial. The person had a history of a positive ANA

at baseline.

There was one report of multiple sclerosis in our open-label experience. That was a woman who had a ten-year history of neurogenic bladder and right-leg weakness. She was seen by a neurologist during this study. She had been in the study for almost 33 months.

The neurologist made the diagnosis on the basis of her symptoms but also on the basis of oligoclonal bands in her spinal fluid. Her MRI was negative. It was the opinion of the investigator that this was a pre-existing condition. In double-blind, we had no optic neuritis and we had one case of demyelating polyneuropathy in a placebo patient. But that was generally our experience with autoimmune disorders.

DR. GIBOFSKY: Follow up, Dr. Holers?

DR. HOLERS: Yes. I just wanted to ask about the extent of the immunosuppression using this drug in patients. Do you have data regarding recall-antigen responses, for instance, to tetanus toxoid, and also is there any data related to the

proportion of lymphocytes, B-cells in particular, and their proportion in patients who are treated with this drug; i.e., is there any evidence of depletion of particular subsets, B-cells and macrophages?

DR. WACLAWSKI: The question about the immune system and, particularly, recall antigens, we had some experience with the use of vaccinations in our psoriasis program which we can have Dr. Vratsanos review for you. But we have also started a study in patients with--it has actually been completed--a healthy-volunteer study looking at the effects of abatacept on vaccination and responses to vaccination including tetanus toxoid.

So I would like Dr. Tay, who has conducted that study, to give a brief summary of that and then ask Dr. Vratsanos to address your other points with respect to what we know from other experiences with respect to T-cell responsiveness in the presence and absence of abatacept.

Dr. Tay?

DR. TAY: We carried out a study in

healthy volunteers to look at two vaccines, the effect of abatacept on two vaccines. The first one was tetanus toxoid and the second was the Pneumovax which is the 23-valent pneumococcal vaccine which contains the 23 polysaccharide antigens.

But, for this study, for the pneumococcal vaccine, we only analyzed for seven of those capsular antigens. Following the recommendation of the CDC, we also used a two-fold increase in levels of specific antibodies as a proof of positive immune response.

In this study, we also looked at the relative timing of the vaccination relative to when abatacept was given.

If I may have Slide 24-3, I would just like to run through the study design to give you a better idea of what it is.

(Slide.)

In the first group, it was just a control group which just received vaccines alone. In the second group, vaccine was given two weeks before abatacept. Typically, it takes about two weeks to

get an immune response and so, essentially, we are administrating abatacept when they have mounted a response already to the vaccines.

In Group 3, we gave the vaccines two weeks after abatacept. Now, abatacept has a half life of about 11--about two weeks. So, in this group of subjects, we are vaccinating them in the presence of relatively high circulating levels of drug.

Then, in the fourth group, if you can notice, we vaccinated them eight weeks after they received the abatacept. In this instance, we are now vaccinating them in the presence of very low level of abatacept. Following that, we then evaluated their response 14 days and then 28 days after they received their vaccinations.

The results indicate that there was a lowering, there was a diminishment, of response in Group 3. These are the subjects that received their vaccinations two weeks after abatacept. But when you look at, or you determine the percent of subjects that were able to respond to the vaccines, we found that abatacept did not inhibit, did not

totally inhibit, the ability of these subjects to mount a two-fold or greater response to either vaccine.

DR. WACLAWSKI: My team has handed me, just for the diabetes question, new or worsening diabetes was 11 reports on abatacept, 0.6 percent, versus 5 on placebo, or 0.5 percent. So the point about the possibility of an instigation of diabetes, we have small numbers but not concerning information here.

DR. GIBOFSKY: I have two quick questions before we break, one for Dr. MacNeil and one for Dr. Vratsanos.

Dr. MacNeil, could you tell us a little bit, explain a little bit more, about infusion reactions, hypersensitivity and immunogenicity of the drug?

DR. MacNEIL: We evaluated infusion reactions as those adverse events, prespecified adverse events, that might be associated with an infusion reaction that occurred within one hour of the infusion. Those were what we called acute

infusion reactions.

Overall, there was 8.9 percent of abatacept subjects who experienced such an event and 5.6 percent of placebo-treated patients. The types of reactions were predominantly dizziness, hypertension, elevated blood pressure, flushing and rash. There were two reactions that would be considered important, very important. One was a report of anaphylaxis. This was a patient who had received placebo therapy for 12 months and, upon receipt of her first dose of abatacept, within minutes, developed hypotension, dyspnea and a rash. That person was hospitalized and recovered uneventfully.

There was also a report in a patient that was described as an anaphylactic-like, anaphylactoid, reaction which we would not consider to meet the criteria of anaphylaxis. This was a person who had been treated for 81 days in the trial and, within the first 24 hours, developed throat tightness and dizziness. That person was hospitalized as well.

There were four patients who had severe reactions that were hypersensitivity reactions which occurred in the first hour. Two of them were reported as hypersensitivity, one as drug hypersensitivity and one has hypotension. All of those patients were discontinued from the trial.

DR. GIBOFSKY: The second question for you is about immunogenicity of the drug.

DR. WACLAWSKI: Our overall experience was that there was a low amount of immunogenicity. Approximately 2 percent of the patients in our trial developed a positive antibody response.

DR. GIBOFSKY: Dr. Vratsanos, you showed us, I believe, four variable calculated DAS 28s in the cohort population and you showed us ACR data as your primary endpoint. Do you have DAS response data on your populations as well?

DR. VRATSANOS: We analyzed multiple EULAR outcomes using the DAS 28 score including patients with improvement, low disease activity as well as remission, defined as a DAS 28 of less than 2.6. In all cases, the proportion of patients achieving

those outcomes was greater in patients treated with abatacept.

May I have Slide 43b-49, please.

(Slide.)

These data come from the trial in methotrexate-inadequate responders at six months and one year. Importantly, at one year, 17 percent of patients on abatacept achieved this outcome of remission according to EULAR criteria versus about 2 percent of placebo-treated patients. The data were similar for the study in anti-TNF-inadequate responders.

DR. GIBOFSKY: Anything further from members of the panel? Dr. Porter?

DR. PORTER: Many of the new biologicals are effective against psoriasis. This does not appear to be the case for your drug. What is the plan for labeling your drug for psoriasis?

DR. WACLAWSKI: We are not seeking an indication for psoriasis today. It is something that is under consideration for development in the future.

Dr. Levy, the head of our clinical immunology team, would like to make a comment as well.

DR. LEVY: Thank you. I would just like to say further that we did conduct some research in psoriasis with this compound in mid to late 1990s before switching our strategic focus to rheumatoid arthritis. The data were very preliminary but, such as they were, there was some preliminary evidence of activity in this disease state and no evidence that the drug might cause a disease flare

DR. PORTER: I see.

DR. LEVY: So, as Tony said, we intend to encourage physicians to prescribe this drug on-label. Psoriasis is off-label. We have no intention to see it there. I just simply wanted just to add that it is-

DR. PORTER: Well, there also must be some negative data. On Page 134 of your document, psoriasis was the only AE that was appreciably more frequent in drug-treated patients during the double-blind period, et cetera, et cetera.

DR. LEVY: I am simply trying to provide you with a fuller picture of the data that is available on the drug in psoriasis.

DR. PORTER: I see. Okay.

DR. GIBOFSKY: Thank you. If there are no further questions of the sponsor, I think the commission will now take a 15-minute break. We are exactly 15 minutes behind but I promise to get us back on schedule before the morning ends.

(Break.)

DR. GIBOFSKY: We will resume the second part of the morning session. At this point, I would like to ask Dr. Keith Hull of the agency to make the FDA presentation.

Dr. Hull.

FDA Presentation

BLA 125118, Abatacept

DR. HULL: Good morning.

(Slide.)

In my presentation today, I will be sharing with you the FDA's review of the safety and efficacy data from the clinical trials of abatacept

in patients with rheumatoid arthritis.

(Slide.)

The proposed indications for abatacept are as follows. Abatacept is proposed for use in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more biologic or non-biologic DMARDs. It is proposed for the indications of reducing signs and symptoms, inducing a major clinical response, inhibiting the progression of structural damage and improving physical function.

It is also proposed that abatacept may be used as monotherapy or concomitantly with methotrexate or other nonbiologic DMARD therapies.

(Slide.)

For today's presentation, I will start with a brief description of the abatacept clinical-development program and a review of the clinical study designs and what was common between the studies. Next I will review the efficacy data for the three proposed clinical indications and then this will be followed by a discussion of the

safety database. Lastly, I will summarize our findings.

(Slide.)

The abatacept clinical program consisted of six randomized, double-blinded, placebo-controlled, trials. The three clinical trials highlighted in yellow comprised the majority of the data used for the efficacy analysis of abatacept. I should also point out that the trials showed here not only used the proposed dosing regimen of abatacept, which I will describe a little later, but it also used lower doses in different regimens.

For the purposes of our discussion, I will identify the individual trials used in the last three digits of the study name. Study 100 was a phase II, 12-month, dose-ranging study with concomitant methotrexate. Study 102 was a phase III, 12-month, trial with concomitant methotrexate also. Study 29 was a phase III, 6-month trial in patients who had failed a TNF-blocker therapy. For the remaining three studies, they consisted of 031

which was a phase III, 12-month, add-on to standard-of-care trial conducted primarily for the collection of safety data. Study 002 was a phase II, 3-month, dose-ranging monotherapy trial. Lastly, Study 101 was a phase II, 12-month, trial with concomitant etanercept.

(Slide.)

All of the studies had several common features in terms of study design. They were all randomized, double-blinded and placebo-controlled. Major inclusion criteria stated that patients need the diagnosis of RA based on the 1987 Revised American Rheumatism Association criteria and also that all patients had to have active disease at the time or randomization despite being on a DMARD therapy.

Active disease was defined as more than 10 swollen joints, more than 12 tender joints and a C-reactive protein greater than 1 milligram per deciliter. Patients were allowed to be on stable doses of prednisone and NSAIDs.

Major exclusion criteria restricted the

enrollment of patients with severe progressive or uncontrolled major-organ disease or serious active or latent infections. In each of the studies, abatacept was administered intravenously as an infusion at Week 0, 2, 4 and then every four weeks thereafter.

Abatacept dosing was either weight-based on a milligram per kilogram basis or by a weight-tiered-based dosing regimen that is being proposed for marketing and is centered around a 10 milligram per kilogram dose. In this weight-tiered-based regimen, subjects weighing less than 60 kilograms receive abatacept 500 milligrams IV. Subjects weighing between 60 to 100 kilograms receive 750 milligrams of abatacept and patients weighing over 1000 kilograms receive 1000 milligrams of abatacept.

(Slide.)

All statistical analysis utilized the modified intent-to-treat principle; that is, including all randomized patients who received at least one dose of study drug. Co-primary endpoints

were tested sequentially with a co-primary endpoint being tested for significance only if the preceding co-primary endpoint was statistically significant.

A Type 1 error rate of 5 percent was maintained for each level of testing. Adjustment for multiple doses of abatacept were performed using global testing followed by pairwise comparisons for the individual doses.

(Slide.)

Categorical endpoints were used for the primary analysis of the improvement of signs and symptoms and the improvement of physical function as follows. Improvement of signs and symptoms used the proportion of patients achieving an ACR 20 response rate at six months. Improvement in physical function used a proportion of patients achieving a clinically meaningful improvement as defined by at least a 0.3-unit improvement from baseline in disability index of the Health Assessment Questionnaire which will be referred to as the HAQ.

Analysis for both the ACR and the HAQ

response rates were preformed using a chi-square test with nonresponder imputation for missing data. The primary endpoint for inhibition of radiographic progression utilized the change from baseline of total erosion score of the Genant-modified Sharp scoring system and, for statistical analysis, used a rank-based nonparametric ANCOVA model with linear extrapolation for missing data.

(Slide.)

Now I am going to tell you some of the specific features for four of the studies. Study 102 evaluated abatacept with concomitant methotrexate in patients who had failed methotrexate alone. This was 12-month study that randomized 656 patients in a 2-to-1 ratio to received either weight-tiered-dose abatacept or placebo. All subjects were also on concomitant methotrexate of at least 15 milligrams weekly.

There were three co-primary endpoints analyzed sequentially in the following hierarchical order. First was the ACR 20 response at six months. Second was an improvement in physical

function as measured by HAQ at 12 months. Third was the inhibition of radiographic progression at 12 months.

(Slide.)

Study 100 evaluated two different doses of abatacept in patients with active disease despite receiving background methotrexate. This was a 12-month study with similar numbers of patients randomized to one of three arms; abatacept 10 milligram per kilogram, abatacept 1 milligram per kilogram or placebo. All subjects were on concomitant methotrexate.

The primary endpoint for this study was the proportion of patients achieving an ACR 20 response at six months.

(Slide.)

Study 029 evaluated abatacept in patients who had failed a TNF-blocker therapy, specifically etanercept or infliximab. This was a six-month study that randomized 393 patients in a 2-to-1 ratio to receive either the weight-tiered-dose abatacept or placebo. All subjects were allowed to

continue stable doses of their nonbiologic DMARDs.

There were two co-primary endpoints which were analyzed sequentially in the following hierarchical order. First was ACR 20 response at six months and the second was an improvement in physical function at six months.

(Slide.)

Study 031 evaluated abatacept as add-on therapy to patients receiving standard of care which could have included both nonbiologic or biologic DMARDs. This was a 12-month study that also permitted the enrollment of patients with comorbid conditions including COPD, diabetes, asthma and CHF.

1441 patients were randomized, again in a 2-to-1 ratio, to receive either their baseline therapy or weight-tiered-dose abatacept or baseline therapy plus placebo. The primary objective of the study was to collect safety data on the use of abatacept and one or more DMARDs in patients with or without comorbid conditions. Exploratory objectives include the improvement in the HAQ

scores at Day 365 as well as some other parameters.

So, in addition to these four studies that I just mentioned, there is another study that I will present a little bit later which assesses abatacept monotherapy without concomitant DMARDs.

(Slide.)

In your briefing packets, you have baseline demographic and disease-activity data for the individual trials. I will present here the pooled data for the four major abatacept trials that I had just outlined.

Baseline patient demographic and baseline disease activities were generally similar across the studies. So you can see from the data the average age was approximately 52 years of age and the majority of patients were female and white. The patients had, on average, a diagnosis of RA for ten years and they had active disease which we can see by the number of swollen and tender joints. 79 percent of patients were rheumatoid-factor-positive and, of the patients taking methotrexate, which was the majority of patients, they averaged 16

milligrams weekly.

(Slide.)

I will now discuss the efficacy analysis of the clinical trials and I will start with the improvement of signs and symptoms.

(Slide.)

This slide presents data from Study 102 which was to evaluate abatacept with concomitant methotrexate. As we can see, a large proportion of patients achieved an ACR 20 at Day 169 and at Day 365 compared to placebo. Higher ACR response rates were also seen at Day 169 and Day 365 compared to placebo.

(Slide.)

A difference in ACR 20 response rates were seen as early at Day 15 and a difference was maintained after Day 365.

(Slide.)

Study 102 also looked at the proportion of patients achieving a major clinical response which is defined as a maintenance of ACR 70 response for at least six consecutive months. So we can see,

from the data, 14 percent of patients in Study 1102 achieved a major clinical response compared to 2 percent of patients receiving placebo.

(Slide.)

We asked whether the clinical improvement in the ACR response rates were due to a subset of the ACR components or if it was more broad-based. The table shows that, on the whole, patients treated with abatacept had a greater clinical benefit than patients treated with placebo for each of the individual components that make up the ACR criteria.

(Slide.)

Up until this point, we have discussed improvement in the patient's clinical response as determined by ACR response rates. However, this slide shows a patient's overall level of clinical activity, as measured by the DAS 28 scoring system, in this case at Day 365. The DAS 28 scoring system is a composite of a patient's sed rate, number of tender joints, number of swollen joints and a patient's global assessment of disease activity.

DAS 28 scores range from 0 to 9.3 with scores lower than 3.2 being considered low disease activity and scored above 5.1 representing high disease activity. So we can see from the data, patients in both groups had a DAS 28 score of 6.8 representing high disease activity.

At Day 365, abatacept-treated patients demonstrated a significant decrease in their DAS 28 scores compared to placebo and they also attained a higher proportion of patients achieving a EULAR-defined low disease activity and a EULAR-defined remission.

(Slide.)

Study 100 compared the 10 milligram dose of abatacept to the 2 milligram dose and placebo. As we can see from the data, a greater proportion of patients treated with the 10 milligram per kilogram dose achieved an ACR 20 response at Day 180 and Day 360 compared to placebo-treated patients. There were also higher ACR response rates in the abatacept 10 milligram per kilogram group compared to placebo.

Of those patients receiving abatacept 2 milligram per kilogram had intermediate responses. Also not shown on this slide but also important is that subjects receiving the 10 milligram per kilogram dose also had a significant proportion of patients achieving a major clinical response compared to placebo-treated patients.

(Slide.)

Currently, RA patients with poor prognostic factors and active disease, despite being treated with methotrexate, generally have a TNF antagonist added to their therapeutic regimen. However, if patients failed this combination, there is no approved alternative affective therapy that is currently available.

The sponsor conducted Study 029 to evaluate the utility of abatacept in RA patients who have failed both methotrexate and a TNF blocker. For this study, patients discontinued the use of the TNF-blocking therapy but they were continued on their background nonbiologic DMARDs.

As shown here, a larger proportion of

patients treated with abatacept had achieved an ACR 20 at Day 169 compared to placebo and higher rates of ACR response were also seen for the abatacept-treated patients.

(Slide.)

This slide shows the DAS 28 scores from Study 029, the TNF-blocker-failure trial. As we can see, again, at baseline, patients had a high disease activity with a DAS 28 score of 6.9. At Day 169, abatacept-treated patients demonstrated a significant decrease in their mean DAS 28 scores compared to placebo and, again, a greater proportion had also achieved a EULAR-defined low disease activity and a EULAR-defined remission.

(Slide.)

The agency is interested in relaying information to physicians about RA therapies that can induce a low disease activity. We are considering what constitutes the best outcome measures for evaluating this.

The sponsor collected data using the DAS 28 scoring system which uses the EULAR definition

of remission as a DAS 28 score of less than 2.6. However, patients with a EULAR definition of remission can still have several swollen or several tender joints.

To, perhaps, better capture the concept of a very low disease activity, we performed post hoc analysis using the DAS 28 scores from the abatacept looking at proportion of patients that achieved a DAS 28 score of less than 2.6 and had no more than one swollen and one tender joint.

(Slide.)

This slide shows the DAS 28 scores from Study 102 at Days 169 and Day 365. At Day 169, a greater proportion of patients treated with abatacept had achieved a EULAR-defined remission compared to placebo. But, using the more stringent criterion that I have just mentioned earlier where patients have a DAS 28 score less than 2.6 and no more than one swollen or tender joint, you can see that, still, abatacept patients had a larger proportion of patients achieving this level of very low disease activity compared to placebo and

similar results were seen at Day 365 with actually a higher proportion of patients, 11 percent, achieving this more stringent definition of very low disease activity compared to placebo.

(Slide.)

Similarly, patients enrolled in the TNF-blocking trial, the Study 029, also demonstrated a great proportion of patients achieving this very low disease-activity criterion that I just mentioned.

(Slide.)

Since the proposed weight-tiered dosing regimen will result in patients within a weight range receiving different doses of abatacept based on a milligram-per-kilogram basis, the agency conducted safety and efficacy analysis from studies using the weight-tiered-dosing regimen based on patient's weight using 10 kilogram intervals.

This slide shows the proportion of subjects achieving the ACR 20 response with the left column breaking down the subjects' weights in 10 kilogram increments. Subjects above this weight

line here were receiving abatacept 500 milligram per kilogram. Subjects in the middle group, between 60 and 100 kilograms, were receiving abatacept 750 milligrams. Those patients above 100 kilograms received 1000 milligrams of abatacept.

The column here that looks green, the second column, shows the approximate abatacept milligram-per-kilogram dose received for the relative 10-kilogram increment on average. As we can see, looking at the response columns, that abatacept-treated patients, a greater proportion had achieved and ACR 20 response than those patients receiving placebo. This is a little bit more easily seen if we look at the point estimate of the differences which were all positive showing an effect of abatacept.

Safety analysis demonstrated similar frequencies of adverse events and serious adverse events between weight intervals and, overall, there does not appear to be a clinically meaningful difference between the extreme of weights using the

proposed weight-tiered-dose regimen.

(Slide.)

Now, I will discuss the analysis for improvement of physical function. Previous studies have validated the use of HAQ scores for measuring improvement in physical function. These studies have shown that an increase in the HAQ score of more than 0.22 units from baseline represents a clinically meaningful improvement.

The sponsor used a more stringent endpoint by analyzing the proportion of patients achieving improvements in HAQ scores from baseline greater than 0.3 units. The data presented here is from Study 1102 which looked at abatacept with concomitant methotrexate. We can see that a greater proportion of patients receiving abatacept have achieved a clinically meaningful improvement in physical function compared to placebo-treated patients.

(Slide.)

The primary analysis for Study 100 used the intent-to-treat population and demonstrated

that a higher proportion of patients treated with abatacept, 10 milligram per kilogram, achieved a clinically meaningful improvement in physical function compared to placebo. Although these point estimates are lower than what was seen in Study 1102, there is still an approximate 18 percent difference between the groups.

(Slide.)

This graph represents the subsets of patients enrolled in the open-label period of Study 100. At Day 360, all patients received open-label weight-tiered-dose abatacept. Similar to what was seen in the ITT population in the previous slide, at Day 360, a great proportion of abatacept-treated patients had achieved a clinically meaningful improvement in physical function compared to placebo-treated patients. This effect was maintained out to Day 720 and 1080 where up to 75 percent of patients were still enrolled in the trial.

One thing that we noticed, and you may be noticing also on the slide, is that the subjects

randomized to placebo never quite reached the level of patients who were randomized to abatacept despite receiving open-label abatacept at Day 360 and we can't explain this finding.

(Slide.)

Now I will discuss the analysis for the inhibition of radiographic progression. This slide shows the mean change from baseline of the total Genant-modified Sharp score. Overall, abatacept-treated patients had a lower rate of radiographic progression than placebo-treated patients.

Although abatacept did not completely inhibit the radiographic progression of RA, it did decrease the progression by approximately 50 percent.

(Slide.)

This slide shows the mean change from baseline of the individual components that comprise the total Genant-modified Sharp score, namely the erosion score and the joint-space narrowing score. I should point out that the erosion score was the

primary endpoint for the study.

As seen in the previous slide, the individual components demonstrate a similar degree of inhibition of radiographic progression with approximately 50 percent decrease in radiographic progression.

I should note also that the primary endpoint was the erosion score and not the total Genant-modified Sharp score.

(Slide.)

Now I will discuss the monotherapy that I mentioned earlier. Up until this point, all the studies I have mentioned have had concomitant methotrexate or other DMARDs in addition to abatacept. Study 002 was a three-month study that compared abatacept monotherapy to placebo in patients without background DMARDs.

The patients enrolled in the study had active RA despite previous DMARD therapy but underwent a 28-day drug washout period prior to randomization. 112 patients were randomized to one of four groups; abatacept, 0.5 milligram per

kilogram, 2 milligram per kilogram or 10 milligram per kilogram and placebo. The primary endpoint was the ACR 20 response at Day 85.

(Slide.)

As you can see, the data demonstrate that the 10 milligram per kilogram dose had a higher percentage of clinical effectiveness with 53 percent of patients achieving an ACR 20 compared to 31 percent of placebo subjects. The abatacept 2 milligram per kilogram dose was intermediate between the two responses and the 0.6 milligram per kilogram dose had no effect compared to placebo.

(Slide.)

To analyze the generalizability of the efficacy results, we performed subset analysis for each of the trials based on the patient's baseline demographics and baseline-disease activities including age, sex, race and weight and the baseline-disease activities of disease duration, the number of swollen and tender joints, C-reactive protein, baseline Genant-modified Sharp score and baseline HAQ scores. Similar clinical responses

were seen between the patient subsets.

(Slide.)

Now I will discuss the FDA's analysis of the safety database.

(Slide.)

The safety assessment was primarily based on the five studies 100, 101, 102, 029 and 031. During the double-blind periods, there were 1,955 abatacept-treated patients representing 1688 person years and there were 989 placebo-treated patients representing 795 person years. The combined number of subjects between the open-label periods and double-blind periods of these studies totals 2688 abatacept-treated patients.

(Slide.)

This slide represents the cumulative exposure of abatacept in all of the RA clinical trials. I would like to draw your attention to the abatacept 10 milligram per kilogram column which also included patients who were receiving the weight-tiered dose regimen.

So we can see here, approximately 1600

patients had received abatacept for more than one year which represented a median of 14 months exposure to abatacept. These numbers provided us with an inadequate database to initially assess the safety of abatacept.

(Slide.)

But, during the RA clinical trials, there were a total of 26 deaths. 16 patients died during the double-blind periods and 10 patients died during the open-label periods. There were comparable numbers of percentages of deaths during the double-blind periods between the abatacept group and the placebo-treated patient.

Of the ten abatacept-treated patients that died, four died from cardiovascular disorders, three were found dead at home, two died from malignancies and one died from infection. Of the six placebo-treated patients, two died from cardiovascular disorders, one was found dead at home, one died from malignancy and two died from infection. Analysis of the individual deaths did not suggest a safety signal from any single type of

adverse event.

(Slide.)

Additionally, eight of the deaths from the abatacept group including the double-blind period and the open-label period occurred during Study 031 which was the study that permitted enrollment of patients with comorbidities. These comorbidities may have contributed to some of the deaths.

(Slide.)

During the double-blind period of the RA trials, 14 percent of abatacept-treated patients had a serious adverse event compared to 12 percent of placebo-treated patients. While there is no individual serious adverse event that occurred in more than 1 percent of patients, overall, there was an increase amount of abatacept-treated patients who developed an infectious serious adverse event compared to placebo-treated patients, 3 percent versus 2 percent.

(Slide.)

During the double-blind periods of the trials, there were a comparable number of

malignancies in both groups which approximated 1.5 percent of abatacept and 1.1 percent of placebo. I should note that these numbers presented here are slightly different than what is in the FDA briefing document and slightly different from what the sponsors presented because we added the malignancies that occurred after the sponsor's cutoff period of 56 days following the last dose of study drug.

(Slide.)

Of the total malignancies, there is a similar proportion of solid-organ tumors between the two groups, 0.7 percent for abatacept and 0.5 for placebo. There were two hematologic malignancies during the double-blind period in the abatacept group and none in placebo--this was the one patient with lymphoma who had Hashimoto's thyroiditis--and there was one case of myelodysplastic syndrome.

(Slide.)

Of the 13 solid-organ tumors seen in the abatacept group during the double-blind period,

there were four cases of lung cancer, two cases of breast cancer and one case each of renal-cell, bladder, ovarian, prostate, thyroid, cholangiocarcinoma and cervical cancer.

The overall malignancy incidence rate was similar between the two groups and comparable to the SEER database. The patients' ages ranged from between 39 and 83 years of age and there was no clear clinical correlation between the development of a malignancy and the number of infusions or the total dose of abatacept and the day of onset after the first dose, or the day of diagnosis.

(Slide.)

During the open-label periods of the trials, there were 47 patients who developed 52 neoplasms. Of the 53 neoplasms, there were 26 malignancies of which there were 13 solid-organ tumors, four lung cancers, two ovarian cancers, two endometrial cancers and one case each of breast, prostate, melanoma, cervical and rectal cancer. There were three lymphomas reported during the open-label periods.

(Slide.)

Because a large part of the clinical experience was during the open-label periods and thus lacked a concurrent control, we asked whether the rate of cancers were increased compared to the general population. To assess this question, we compared the rates of the observed malignancies to those expected in the age- and sex-matched control patients in the SEER database.

As we can see by the standard incidence ratio here, there was no increase in the overall relative risk for developing a malignancy associated with the use of abatacept. However, the relative risk of developing lung cancer was two-fold higher in patients treated with abatacept and almost four-fold higher for the risk of developing a lymphoma.

You will also note that there is almost a three-fold increased risk here for thyroid and ovarian cancer but these contain a very small number of cases and it is difficult to draw firm conclusions.

(Slide.)

So if treatment duration or exposure to abatacept was related to the induction of malignancies, then we would expect to see an increased frequency of malignancies the longer patients are treated with abatacept. To answer this question, we looked at the rates of malignancies per 100 patient years in six-month intervals and saw no increase in the frequencies of malignancies relative to the increasing amounts of exposure.

Of course, longer-term studies will be needed to fully assess the risk since cancers can remain undetectable for several years.

(Slide.)

There are three potentially concerning malignancies that we felt warranted closer analysis; lung cancer, breast cancer and lymphoma. A review of the malignancy data showed that there were a total of eight cases of lung cancer in abatacept-treated patients four of which occurred during the double-blind period when there was none

in the placebo group.

Seven of the eight patients had a history of smoking. All were over the age of 60. A retrospective analysis of the cases showed that two of the patients had radiographic evidence of lung cancer at baseline.

For because and lymphoma, there was a concern because of the preclinical studies that demonstrated an increased rate of mammary tumors and lymphomas in mice, it was subsequently believed to secondary to abatacept-induced chronic immunosuppression and reactivation of the retroviruses, murine mammary-tumor virus and murine leukemia virus.

The idea that the increased number of tumors was seen in the mice was due to reactivation of retroviruses was further supported by one-year studies in which cynomolgus monkeys were exposed to much higher doses of abatacept than that intended for human use and there was no report of cases of lymphoma.

An additional concern was the known

increased risk of lymphoma in patients on immunosuppressive drugs or patients with rheumatoid arthritis.

(Slide.)

In addition to the SEER database, it is useful to have a disease-specific comparator group to interpret the rate of lung cancer in the abatacept-treated patients since reports suggest that there is an increased risk of lung cancer in patients with RA.

So, to see that, we looked at three such databases that were evaluated and looked at the eight cases observed in the abatacept trials and saw that this was in line with one of the point estimates of the British Columbia database but still higher than the point estimates of two of the other RA cohorts but within the 95 percent confidence intervals.

(Slide.)

During the course of the trials, there were three cases of breast cancer, two of which occurred during the placebo, the double-blind,

period and, at the same time, there were two in the placebo group. But there were three cases overall with an additional case occurring during the open-label period.

The rates were comparable between the two groups and the current evidence does not suggest that abatacept increases the rates of breast cancer.

There were a total of four cases of lymphoma reported in the abatacept patients, one during the double-blind period and three during the open-label period. As previously discussed, that represents a four-fold higher rate than that seen in the general U.S. population. However, it should be noted that there is an increased rate of lymphoma in patients with RA and particularly those with high disease activity.

(Slide.)

Since abatacept is an immunosuppression agent, we were concerned that it would also increase the risk of infections. So we looked at the frequency of serious infections. As I have

mentioned previously, overall, there was an increased rate of infectious serious adverse events in patients with abatacept, 3 percent compared to placebo, 2 percent. The most common infections included pneumonia, cellulitis, urinary-tract infection and bronchitis.

(Slide.)

The term infections of special interest here is a subset of 377 predefined infections thought to represent clinically significant disease. These include common bacterial infections such as pneumonia, atypical infections such as tuberculosis and fungal infections such as aspergillosis as well as viral infections such as herpes.

As shown in the slide, overall, there was an increased rate of infections of special interest in patients receiving abatacept, 10 percent versus 7 percent of placebo. Those that were more common in patients receiving abatacept were all types of herpes infections and also pneumonia which occurred at almost a two-fold higher rate in patients

receiving abatacept.

Also included individually in these infections of special interest are the individual opportunistic infections. Overall, there didn't appear to be an increased rate of opportunistic infections in abatacept-treated patients but I have listed several of the opportunistic infections here; herpes zoster, which occurred in 2 percent in each group, oral fungal infections, tuberculosis, which occurred in two cases in the abatacept-treated patients and one in the placebo patient, and aspergillosis which occurred in the abatacept group.

(Slide.)

So, when RA patients have active disease despite standard-of-care therapy, rheumatologists generally add on a new agent without necessarily stopping the old regimen. Therefore, it is possible that physicians would add abatacept to other biologic DMARDs. To better understand the safety of the combinations, we examined the data on the safety of abatacept with concomitant biologic

DMARD therapy.

(Slide.)

There was a total of 204 patients that received abatacept and concomitant biologic RA therapy during the double-blinded periods which represented 173 person years of exposure. The majority of the patients were from Study 101 and Study 031. Of all the 204 patients, the majority were on a TNF blocker, over 90 percent, with the remaining being on anakinra.

Study 101 compared the combination of abatacept, 2 milligram per kilogram, per etanercept to placebo plus etanercept alone.

(Slide.)

For patients receiving a biologic RA therapy, the rate of serious adverse events was higher in patients receiving abatacept than placebo, 20 percent versus 90 percent. Some of this increased rate was due to an increased number of infections in neoplasms. Additionally, patients receiving abatacept plus a biologic RA therapy reported more serious adverse events than patients

receiving abatacept in the nonbiologic RA therapy, 13 percent, so 20 versus 13.

A similar trend was also seen for the overall adverse events.

(Slide.)

So in addition to looking at the safety of abatacept in concomitant biologic RA therapies, we also analyzed the safety of abatacept with non-biologic DMARDs. If you recall, Study 031 had added abatacept therapy to a patient's current regimen, thus providing an opportunity to collect data on the safety of abatacept with a broad range of commonly used RA therapies.

So you can see from the slide, a greater proportion of abatacept-treated patients reported a serious adverse event when they were on a biologic RA therapy, 22 percent versus placebo, 13 percent.

In reference to Dr. Felson's question earlier, here are the people on anakinra which doesn't show an increased rate in patients on anakinra and abatacept compared to placebo.

Also, you can see from this slide that

patients who were receiving abatacept didn't have an increased serious adverse event reported compared to patients on placebo plus a nonbiologic DMARD group, 12 percent in each group. Of course, this is only from Study 031.

There is one exception to that and that is the addition of abatacept to leflunomide which reported 25 percent of patients having a serious adverse event which is comparable to what was seen with abatacept in biologic RA therapy. Further analysis of these, however, showed that there was no single adverse event that was responsible for the higher rate.

(Slide.)

Since abatacept is an exogenous protein, infusion-related adverse events were a potential concern. The sponsor prespecified a subset of adverse events, for example allergic-type reaction or hemodynamic events that, if reported within a 24-hour period following the infusion of abatacept, they were categorized as being infusion-related.

This slide shows that infusion-related

reactions within one hour post-infusion was greater in patients receiving abatacept, 9 percent of patients, compared to 6 percent of placebo-treated patients. Similar results were seen looking at infusion-related reactions out to 24 hours, or 23 percent of abatacept-treated patients had reported infusion reaction compared to 19 percent of placebo-treated patients.

Overall, there were two cases of anaphylactic type reactions reported in patients receiving abatacept.

(Slide.)

The potential for immunogenicity is expected with the use of any therapeutic protein and the development of an immune response against abatacept, meaning the whole molecule as well as the CTLA4 portion of abatacept, was approximately 1.6 percent for all patients receiving abatacept. 5.8 percent of abatacept patients who had discontinued therapy for at least 56 days developed antibodies to abatacept.

However, there is no increased incidence

of immunogenicity observed in patients following missed doses compared to patients with uninterrupted treatment. There did not appear to be a correlation between antibody development in the safety or efficacy of abatacept although it is difficult to reach firm conclusions since there are such very low numbers of patients who developed antibodies to abatacept.

In addition to the immunogenicity, we also looked at changes in clinical laboratory values including blood chemistries and hematologic labs and there seemed to be no clinically meaningful differences between patients in either group.

(Slide.)

To quantify autoimmune symptoms in disorders, the sponsor used a set of prespecified MedDRA codes that presented symptoms or diseases that could be related to autoimmunity. During the double-blind period, 3 percent of abatacept-treated patients reported an autoimmune-related adverse event compared to 2 percent of placebo-treated patients during the double-blind period.

Most of these were of mild to moderate in severity and the most common symptoms were associated rheumatoid arthritis and included things such as keratoconjunctivitis sicca or Sjongren's syndrome. The only autoimmune-related adverse event that wasn't associated with RA that occurred in a greater proportion of patients treated with abatacept was psoriasis and that was 0.5 percent of patients on abatacept versus 0.l percent of patients treated with placebo.

To answer Dr. Porter's question, there is more information in the FDA briefing document on it in Section 5.8.1 on Page 117.

(Slide.)

Antinuclear antibodies and antibodies of double-stranded DNA were measured in the double-blind periods to assess the potential for autoimmune reactions due to abatacept. As we can see from this slide, 10 percent of patients treated with abatacept had developed an antinuclear antibody while 11 percent of patients treated with placebo developed an antinuclear antibody.

Also, 3 percent of patients treated with abatacept had developed an antibody to double-stranded DNA while 5 percent of patients treated with placebo had developed double-stranded antibodies. So, overall, the autoimmune-related safety did not suggest that the abatacept is associated with clinically important risk of developing autoimmune disorders.

(Slide.)

Patients with comorbid conditions are often excluded from clinical-development programs and, as a result, unforeseen safety problems can occur once the drug is marketed in the general population. In Study 031, the sponsor permitted the enrollment of patients with comorbid conditions including COPE, diabetes, asthma and congestive heart failure. There is no apparent increase in the adverse events or serious adverse events of diabetes, asthma or congestive heart failure, but there was for patients with COPD where adverse events were reported in 97 percent of abatacept-treated patients versus 88 percent of

placebo-treated patients.

These included respiratory adverse events which were approximately two times more common with abatacept, 43 percent versus 24 percent, and serious adverse events were also more common with approximately 27 percent of patients treated with abatacept reporting a serious adverse event compared to 6 percent of placebo.

These included things such as COPD exacerbation and respiratory infection. There were no reported deaths in patients reporting a serious adverse event who had COPD.

(Slide.)

So, in summary, the studies presented here show abatacept treatment-associated difference regarding improvement in signs and symptoms, improvement of physical function and inhibition of radiographic progression. There was a higher rate of serious infections in patients with abatacept, especially with patients receiving concomitant TNF-blocking agents.

Overall, malignancy rates were not

substantially different between abatacept and placebo-treated patients. However, abatacept-treated patients had more cases of lung cancer and the rate of lymphoma was higher than expected compared to the general U.S. population.

Infusion-related reactions were observed including hypersensitivity reactions and two cases of anaphylaxis. Lastly, patients with COPD treated with abatacept had a higher incidence of adverse events and serious adverse events, particularly respiratory disorders.

DR. GIBOFSKY: Thank you, Dr. Hull.

Before we go into discussion of the presentation, there are two housekeeping items. The first is if there is any member of the public who is here to testify in the next hour during the Open Public Hearing, please make yourself known to Ms. Clifford, to my left, so that you can be scheduled and your materials appropriately recognized.

The second is I am having a rare Cole Porter moment listening to Dr. Daniels speak of

a-ba-TA-cept and you speak of a-BA-ta-cept. So I am wondering if we can have a definitive statement between O-REN-cia and O-ren-CI-a as well for the record and for the future.

DR. HULL: I will defer to them.

DR. GIBOFSKY: I suspect they defer to you, but that is quite fine.

DR. WACLAWSKI: A-ba-TA-cept is what we have been using.

Questions from the Committee to FDA

DR. GIBOFSKY: Questions from the committee on this elegant presentation? Dr. Ilowite?

DR. ILOWITE: Did you look at the autoantibodies or anti-abatacept antibodies in relationship to concomitant methotrexate or not?

DR. HULL: I didn't look at that specifically but, perhaps, someone from Products has with the autoimmune antibodies.

DR. SIEGEL: Probably not. The rate of antibody formation is fairly low, 1.6 percent overall. Since the vast majority of the patients

in the clinical development program were receiving concomitant methotrexate, we didn't specifically break this out.

I wonder if Bristol-Myers may have more information.

DR. WACLAWSKI: The question is whether there was a tendency towards more antibodies when patients were not on background methotrexate. We would just refer to the monotherapy study which I believe, although it was a phase II study and didn't use the most sensitive assay that we developed for phase III, I believe Dr. Haggerty will confirm that there were no antibodies in that study detected. So it didn't appear, based on that data, that the presence of methotrexate was necessary to retain a low level of immunogenicity.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: A question on COPD. The rates that you talked about were higher than the placebo adverse events in patients with COPD?

DR. HULL: Yes.

DR. FELSON: I mean, you would expect a

lot of respiratory exacerbations in any case.

DR. HULL: Right.

DR. FELSON: So these were comparatively higher.

DR. HULL: Yes.

DR. FELSON: Have you or the sponsor considered labeling considerations? There was a 28 percent rate of serious adverse events in patients with COPD. That is really high.

DR. HULL: Yes. We have considered putting it in the label.

DR. FELSON: Okay.

DR. GIBOFSKY: Further discussion or questions? None. Quite succinct and appropriate.

Open Public Hearing

DR. GIBOFSKY: Are there any individuals from the public who are here to testify?

Hearing none, I think we will adjourn for lunch at this point. We will be back--yes, Dr. Weiss?

DR. WEISS: I am just wondering if, Dr. Elashoff, you still were interested in any comments

from FDA regarding studies in U.S. versus non-U.S. populations and if this would be an opportunity to just have a brief comment about that.

DR. GIBOFSKY: We always welcome questions of questions. Would you like to make that presentation, Dr. Weiss?

DR. WEISS: Well, not so much a presentation, just to note and I would invite anybody else from the agency as well to comment, that there is no specific, certainly, regulation or that much in terms of general guidance about where patients from clinical trials should come from based on region of the country.

It is certainly important to be able to understand if much of the database comes from studies conducted overseas or not from the United States, the ability to generalize those data to United States populations. We have had not so much in RA trials but in many other diseases where, for various reasons, the bulk of the clinical efficacy data come from studies overseas, in Europe, for instance.

There are potentially important differences with respect to demographics, with respect to the natural history of the disease and particularly with respect to concomitant therapies and standards of care that are important considerations and that is always part of the discussions with our sponsors and end-of-phase-II meetings to be able to understand what those differences might be and whether or not they would be important in terms of generalizing the data.

DR. GIBOFSKY: Thank you, Dr. Weiss.

Any further questions or discussion on the point just raised by Dr. Elashoff earlier and commented on by Dr. Weiss? Okay. Hearing none, we will adjourn for lunch. We will reconvene at 12:45. I will ask the members of the committee to remain here and we will go over, as a group, to the lunch area which is a new innovation for this committee.

So we will resume here at 12:45. Members of the committee, please do not discuss this morning with anyone outside the membership of the

committee unless it is the pronunciation of the name of the drug.

(Whereupon, at 11:40 a.m., the proceedings were recessed to be resumed at 12:45 p.m.)

A F T E R N O O N P R O C E E D I N G S

(12:45 p.m.)

DR. GIBOFSKY: Can I invite the members of the people and the agency staff to take their seats so we can resume for the afternoon, please.

Discussion of Questions

DR. GIBOFSKY: We have heard the presentations from the sponsor this morning and also from the agency. At this point, we have received a number of questions to the committee for discussion and ultimately for a vote on one of the issues.

I would like to encourage everyone to participate in the discussions. I, frankly, find the discussions and the information that comes out of the discussions even more meaningful than a vote, a straight up or down vote. So let's get right to it.

The first issue is that we have heard about three randomized placebo-controlled studies of abatacept and RA. We have evaluated a proposed weight-tired dosing regimen and two studies which

evaluate a fixed dose of 10 milligram per kilogram. One study looked at monotherapy with abatacept and four studies looked at abatacept as an add-on to other agents.

Three of these studies followed the FDA guidance document on RA that we all received as part of our materials with particular reference to how it relates to the duration of the placebo-control period and the nature, the endpoints, primary and secondary.

We are told that, and as we heard in the presentations from both the sponsor and the agency, that abatacept treatment showed effect on signs and symptoms compared to placebo as evaluated by ACR criteria, radiographic progression, as evaluated by the modified Genant-Sharp score and physical function as evaluated by the HAQ disability index, all of which have been observed, the ACR 20s. We also saw some data on 50s and 70s. We saw DAS data as well.

So the first issue is efficacy and we are asked for our feelings about and our opinions on

the strength of evidence regarding the demonstration of efficacy of abatacept in the treatment of patients with rheumatoid arthritis.

Dr. Felson, let me impose on you to begin the discussion.

DR. FELSON: I think it works.

DR. GIBOFSKY: Thank you. Can we have the next question? Are there any particular concerns about study design, methodology, statistical analysis? Dr. Elashoff?

DR. ELASHOFF: With respect to ACR 20, all three of the studies show an effect on ACR 20. There are two studies that show an effect on HAQ but there is only one study, as near as I can tell, that has X-ray evidence and I think that is the one with methotrexate.

So the issue is, and it is really more a medical issue, can the fact that we see an effect on X-ray results in one study with methotrexate be extrapolated to using this drug with other background DMARDs because, otherwise, this is just one study with one particular background thing.

DR. GIBOFSKY: I won't answer the question directly, just by way of some additional information for you. Methotrexate is, of course, the DMARD that is used most widely in clinical rheumatology. Patients who don't tolerate methotrexate are, of course, often offered other disease-modifying agents and patients who have incomplete responses to methotrexate are frequently stepped up to a biologic, as you know.

But as to the issue of extrapolatability of the radiographic data with methotrexate to other agents, I think that is an open question.

Dr. Finley, would you care to comment on that?

DR. FINLEY: No, because I am not an X-ray expert. But I would want to just suggest that that is something that, obviously, I would assume the sponsor and the agency will look at in the open-label and postmarketing piece should that come to pass. But I am just thinking about the first question about efficacy and am struck by the impressive nature of how it continues out. The

initial effects seen in the first weeks then are continued through the end of the first year even in those who haven't responded to previous biologics or methotrexate.

DR. GIBOFSKY: Maybe we can have someone from the agency comment on the radiographic data to the extent that the magnitude of the observed difference was in just one component of the Sharp score, erosions, rather than joint-space narrowing in one of the other studies; isn't that correct?

DR. SIEGEL: I believe the data show a similar percent decrease in total Sharp score as in each of the components, joint-space narrowing and erosion score.

DR. GIBOFSKY: I'm sorry; I was asking more in the abstract to what extent you look at the total score as opposed to the individual components.

DR. SIEGEL: Obviously, we looked at the total Sharp score as well as each of the components. If a product only showed benefits for one component and not the other, we would be

concerned and look into that further. But, so long as the effects are similar between the two, there is no reason to think that it would lack the clinical benefits associated.

DR. GIBOFSKY: And you are comfortable to--as Dr. Elashoff points out, that this has only been demonstrated in one study.

DR. SIEGEL: Right. I am not sure exactly the best way to approach this. To get claims of efficacy, it is necessary to have substantial evidence of efficacy. For a new product in a new disease, generally, that means reproduction of benefits in at least two trials. However, once we have evidence, substantial evidence, of efficacy in one area, when you look at other areas that are related, you don't necessarily require two studies.

With respect to radiographic progression, a single study which is large and robust and showing a substantial benefit, we have not always required that that be reproduced in a second study.

DR. WALTON: This is a circumstance where we can consider a claim of demonstration of benefit

using information regarding the product in a related aspect. But, ultimately, I think, for that question, we are looking to you to advise us whether you find that data in the totality of the evidence here convincing for that aspect of potential benefit.

DR. GIBOFSKY: Perhaps we should discuss the specifics, then, of signs and symptoms as one category, radiographic progression in another and physical function.

Would that be appropriate, Dr. Elashoff?

DR. ELASHOFF: Yes.

DR. GIBOFSKY: So, based on Dr. Felson's comments, is there anyone who is concerned, or any objection, to the demonstrated efficacy on signs and symptoms? Apparently not. What about physical function? Apparently not. So that leaves us with radiographic progression. Is there anyone who is uncomfortable with the present data supporting a claim of improving structural, or delaying the progression of structural damage?

Dr. Elashoff?

DR. ELASHOFF: I am going to at least abstain on that because I don't know--I don't have a feel for the extent to which you can extrapolate from one background drug to another in that--I mean, it certainly seems to work in that one study. But whether assuming that it works if you have methotrexate as the background versus something as the background, I don't have enough personal knowledge to go further on that.

MS. MALONE: I have a question as to when this drug was used concomitantly with methotrexate and/or the anti-TNF, were those dosages of the methotrexate and the anti-TNF maintained?

DR. GIBOFSKY: Can Dr. Daniels or someone from the sponsor's team respond to that?

DR. WACLAWSKI: In general, the studies were designed to have a stable background of methotrexate which was considered to be an adequate therapeutic dose for the treatment of RA and that would be maintained until at least the six-month time point when the signs and symptoms endpoint was assessed and then, subsequently, for the next six

months of the control trial, there was some flexibility in adjustments of those background doses.

MS. MALONE: Do you know what the dose of the methotrexate was, in general?

DR. WACLAWSKI: The average dose was 16 milligrams per week.

DR. GIBOFSKY: Dr. Holers.

DR. HOLERS: I think one of the things that limits my own perspective of this with regard to its overall effects on progression might be a general concept and I am not sure we really understand why this drug works. I mean, there is clearly evidence, based on preclinical models, and we have a conceptual framework that was nicely presented. But the biomarkers that would address the question of do you see the desired effect, there are no changes, I guess, in serum-cytokine levels that we could address. There are no changes in rheumatoid factor that we could see. And there are not changes in the distribution or activation of lymphocytes in the periphery that really address

the question of is this acting the way we think it is.

DR. GIBOFSKY: There is significant horizontal nodding of heads behind you that you can't see. Would anyone who is doing the nodding care to comment on Dr. Holers.

DR. HOLERS: I would be surprised if there wasn't.

DR. DANIELS: We obviously collect a lot of efficacy information including some surrogate serological markers in our studies. Because of that, we take a very conservative approach as to what we prespecify. We will do statistical testing versus what we just use as exploratory analysis.

Since Dr. Elashoff asked a specific question about the statistically significant around our cytokine, we actually went out over lunch--if you can just take up the slide that we have here, 44b-67.

(Slide.)

What you can see is that, in this one study which is a study in people with--this is the

study at six months in people who had incomplete responses to anti-TNF therapy. For these four cytokines, the ones that we presented, there are statistically significant differences. The rheumatoid factor is the least significant, if you look at it, as far as by eye. It is statistically significant by eye.

But I think one of the interesting points, and Dr. Vratsanos emphasized that, in this patient population at six months who are actually relatively severe along that scale--they have DAS scores of 6.8 at baseline--that 8 percent of the patients who were RF-positive in the abatacept treatment arm became RF-negative.

Again, the way I view that is that is really a significant change in that person's serological profile.

DR. HOLERS: Do you have data with regard to anti-CCP antibodies or sertroline-specific antibodies?

DR. DANIELS: We have some studies under way right now in very early rheumatoid arthritis in

we are collecting CCA. But we don't have it for this patient population.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Do you have any data on the correlation of clinical response with any of those parameters?

DR. VRATSANOS: We were not able to identify an baseline clinical parameter that predicted an ACR 20 response. We conducted a logistic regression analysis using baseline values of various cytokines as well as a comparison of the changes from baseline to three months in terms of predicting the response at six months.

The only variable which predicted an ACR 20 response is one that is not surprising and that was patients who decreased their CRP at three months were more likely to have an ACR 20 response at six months.

DR. GIBOFSKY: Any further question or discussion? Dr. Holers, anything further? Dr. Ilowite?

DR. ILOWITE: I guess I have a question

for the FDA as to what the standard claim for inhibiting radiographic progression for a novel molecule versus another, let's say, TNF inhibitor and wouldn't the standard be--I am assuming the standard is higher for a novel molecule.

In other words, to make the claim that you have effect on radiographic progression, if it is seen in two TNF-inhibitors and there is a third TNF-inhibitor that comes along and demonstrates it in one study, would that be more likely to meet the standard of the FDA for making that claim than a brand-new novel molecule?

DR. WALTON: I think that, for the biologics, it is relatively new to have multiple agents in a class. The biologics are still more likely to be individual agents. We have a few classes with multiple agents. But, even where we do have multiple agents in the class, we have learned that one has to be very, very wary about extrapolating between them until we have a lot of experience with them and we can be sure that they really are the same because we also have agents in

a class where there are suggestions that there are differences in behavior, whether that is due to the exposure based upon different regimens or intrinsic differences between the agents. We can't always know.

So we do tend to be very wary about extrapolating from one agent to another. So I am not sure that we would necessarily regard there being a different standard, rather that we can look at the totality of the evidence for the agent and we would be longing to understand whether the evidence is sufficient, whether one can draw strength from the different kinds of assessments across the kinds of assessments so that seeing the signs and symptoms effects, a treatment-associated effect, and signs and symptoms in multiple studies can provide you with confidence that, even though the radiographic changes have been observed in just a single study, nonetheless, that is a reliably believable effect or whether you would feel that that was not sufficient.

DR. GIBOFSKY: Ms. Malone.

MS. MALONE: This question is really not in line with that but I am wondering if the sponsor is anticipating the prescribing of this drug only after failure with methotrexate and anti-TNF or do they foresee that it would more of a first-line?

DR. WACLAWSKI: Our clinical program is based on studies in patients that have an inadequate response to existing therapy. So, in that sense, it would be intended to be used based on the data we have today in patients who have had an inadequate response to either methotrexate or related DMARDs or the TNF-blocking therapies. So that is our intended patient population for the studies.

Dr. Gibofsky, I just wanted to come back to one other point which was, because our presentation ran over, we didn't have a chance to let the committee know what consultants we had here today. So, for example, I wanted to be sure you knew Dr. van der Heijde, Dr. Genant. If there are questions about inhibition of structural damage, and so forth, we can draw upon them.

I can just show you the slide quickly, if you would just tolerate for one second so the committee knows who is here. Dr. Roger Cohen, who is the director of Phase I Programs and a member of the Thoracic Oncology Team at Fox Chase. Dr. Genovese, a clinician and rheumatologist and familiar with abatacept in the clinical program. Princy Kumar, who is the Chief of the Division of Infectious Disease at Georgetown. Dr. Genant I already mentioned. Dr. Hochberg who is an epidemiologist and rheumatologist. And, of course, Dr. van der Heijde who is well familiar with various studies of agents with structural damage. So just for completeness so you were completely aware.

Thank you.

DR. GIBOFSKY: Dr. Siegel?

DR. SIEGEL: There is another aspect to Ms. Malone's question that I just wanted to comment on which is the question of product being approved in patients who failed standard of care, DMARDs or patients who were just being started on a DMARD.

The usual pattern that we have seen with new biologics is that, when those biologics are first being explored, we don't know what the toxicity will be. So it is prudent to test them in patients who have already failed DMARD because those are people who potentially could benefit from it and who don't have other available therapies. So, oftentimes, the initial clinical development program is in patients who failed a DMARD.

In an effort to prove, the sponsor will often go out and do a study in new, early-stage rheumatoid arthritis and demonstrate that it is safe and effective there. Then they get the indication broadened for use in patients with early rheumatoid arthritis.

This doesn't necessarily mean that the safety and efficacy are expected to differ in the early patient population but it is, nonetheless, a reasonable way to develop a product when you don't know what the safety will be. Then, after it has been on the market a few years and you have a better feeling about the safety and postmarketing

experience, then, to expand the indication.

I don't know what is in mind for Orencia, but that has certainly been the pattern for other products that we have overseen.

DR. GIBOFSKY: Ms. Malone?

MS. MALONE: The concern that is on my mind is just that if someone is taking this new product and also a biologic and/or methotrexate for a long period of time, I mean that is a lot of chemical. After the person is starting to get a good response, I am just wondering, will the other--like the anti-TNF that was not working alone initially--start to be withdrawn gradually?

DR. WALTON: Maybe I could start, but I think we will want to hear from the sponsor as well. We, the FDA, that is, presented data that safety of co-administration with biologics has not been establish for Orencia. So we clearly have concerns about the safety of its use with other biologics.

That experience seemed to be different than with non-biologic DMARDs like methotrexate and

so on.

DR. WACLAWSKI: Just to confirm that that is our assessment as well, is that abatacept should not be used in combination with biologic therapies at this point primarily because, although it is a small experience, it is shown us an increased risk of those infections you are concerned about. Also, we haven't seen enough evidence that, added to a biologic, there is going to be a substantial benefit. So I think we are fairly consistent in that view of the data.

DR. GIBOFSKY: Dr. Elashoff?

DR. ELASHOFF: Along those lines, the ACR 20 curve seemed to pretty much come to a plateau around two months or so. Would one, then, think that people who had not shown an ACR 20 response by about two months should stop taking abatacept and try something else?

DR. WACLAWSKI: We have a limited experience in patients that have taken abatacept up to three months, have had a response and then were withdrawn from drug and monitored afterwards for an

additional three months.

I am going to have Dr. Vratsanos give you specifics on that data but there is some information there that can help response to that comments.

Dr. Vratsanos?

DR. VRATSANOS: I think Elashoff's question was whether the ACR 20 response should be used to guide treatment decisions about continuing abatacept. We have limited information in this regard. Importantly, in our phase III trial, while the ACR 20 response did appear to--or I should say most patients had a response within three to four months, more substantial responses like the ACR 50 and 70 tended to increase over time, particularly from six to 12 months.

So, in our view, that decision is best left to the physician and the patient based on their individual response.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Actually, I think that wasn't Janet's question. I think we were trying to get

some guidance for the clinician that might be incorporated into labeling about how long you try this before you give up. It wasn't about people who were already responding. It was about people who have been on it for a couple of months and who have not responded. How long do you keep going?

What she suggested was that there seemed to be a plateau where there weren't additional people added which suggests that you sort of know after two months which would be, what, four infusions or something, whether this is going to work or not.

DR. VRATSANOS: Overall, I don't think we have enough information to provide to physicians at this time. I think, while the ACR 20 is an important outcome, other important outcomes did tend to increase over time. So I would be concerned that even a two-to three-month trial would be insufficient time to really see the maximum effect with this drug.

DR. WACLAWSKI: This is the type of question where I think we would like to have a

comment from Dr. Genovese who has experience with the program. He is a rheumatologist. He has treated patients. Perhaps, we can ask Dr. Mark Genovese to provide his comment with respect to how he would use abatacept in his patients.

DR. GENOVESE: I think it is a good question. The reality is not all patients respond within the first 15 days. We have seen patients in a number of the double-blind, placebo-controlled, trials that, in fact, do take the period of three or four months to have a response.

My personal bias would be, since it is a chronic disease and not all patients respond quickly, that probably the use of four or five infusions, if it is given at time-point 0 and at two weeks and again at a month, a month later and the following month, that would be a total of five infusions over approximately 12 weeks.

If you haven't had a response at that point, I think it is probably reasonable to move to a different therapy. But I would give it at least that period of time to show efficacy.

DR. GIBOFSKY: The question asks us to discuss the strength of the evidence for the three categories that we have discussed. I think we are all comfortable with the three. I think we are certainly comfortable with the evidence on signs and symptoms. We are comfortable with the evidence on physical function.

I think if there is any disquiet, it is on the strength of the evidence--not the evidence; the strength of the evidence--on radiographic progression because it is based on one study of 391 individuals as shown in the slide.

Perhaps, since Dr. van der Heijde is here, I would be interested in hearing from her whether the response can be categorized in terms of duration of disease. These were individuals, as I recall, with a disease duration of about nine years in that study and yet there are some analyses looking at response as a function of duration of disease.

So I would be interested in hearing about the radiographic inhibition as a function of

duration of disease.

DR. VAN DER HEIJDE: What you see in this trial is indeed quite a long disease duration, that there is a significant inhibition of radiographic progression treated with abatacept on top of methotrexate compared to the patients with methotrexate alone.

If you look for the variation, if you have subgroup analysis for the different disease duration and then the effect of radiographic progression, that was similar among the different subgroups. What we saw, if you calculate the progression rate that these patients had before they entered the trial, that was rather high and that was really reduced within the trial periods.

DR. GIBOFSKY: I want to be sure I understand. The magnitude of inhibition by abatacept is the same, roughly the same, despite the disease duration. So someone with disease duration of less than two years could expect the same degree of structural inhibition as someone with nine years.

DR. VAN DER HEIJDE: We could see a slight, on the subgroup analysis--it is 43b-76.

(Slide.)

That is showing the mean changes in the total radiographic-progression scores at one year and you look at patients with shorter disease and up to longer disease, you see, in all cases, the effect. It seems a little bit better in the patient with early disease, but it might also have to do with how you assess the radiographs. It is rather consistent over all disease-duration groups.

DR. GIBOFSKY: Any further discussion on Question No. 1, the strength of the evidence? Dr. Holers?

DR. HOLERS: Sorry; could you bring that slide back up again? Could you discuss the issue of rheumatoid-factor positivity and negativity at baseline?

DR. WACLAWSKI: Dr. Vratsanos?

DR. HOLERS: My understanding is the request is for labeling for seropositive and seronegative RA.

DR. VRATSANOS: The treatment effect for abatacept was smaller. In the case, it was lower for the X-ray outcome. For signs and symptoms and physical function, efficacy was consistent in both rheumatoid-factor-positive and rheumatoid-factor-negative patients.

In this trial, there was about 10 percent of the population that was rheumatoid-factor-negative. Consistent with the published literature, we saw less progression of structural damage in the rheumatoid-factor-negative group compared to the rheumatoid-factor-positive group.

So it was, in essence, more difficult to see differences between the groups given the lower degree of baseline change.

DR. GIBOFSKY: Anyone else have any questions, comments? Dr. Elashoff?

DR. ELASHOFF: Well, based on that slide, it doesn't look like enough negative patients were studied to make any conclusions at all. So, if one were insisting that, across the three studies,

there was real evidence for use in that subgroup of patients, it doesn't look like there are enough patients in that subgroup to address that question. One is just sort of assuming that results for the positives extend to the negatives.

DR. GIBOFSKY: Response?

DR. WACLAWSKI: I would like to have Dr. Vratsanos first respond to that with respect to the degree to which this patient population represented the general RA population and, again, keeping in mind that there are many, many different subgroups that have been analyzed with sometimes small numbers of patients.

Dr. Vratsanos?

DR. VRATSANOS: The number of rheumatoid-factor-negative patients was small. It is important to realize that multiple subgroup analyses were performed not to, say, statistically test efficacy within particular subgroups but to see consistency of effect across multiple patient populations.

DR. ELASHOFF: The comment wasn't intended

to address the question of whether the two are consistent or not because the sample size is small so you can't address that. But, to address the question of whether you can sort of separately say that the drug works for the negative patients when so few negative patients are looked it--if you are just going to say, in general, it works for RA patients, then you don't have to insist on specific evidence for every subgroup.

If somebody is trying to say it works for both of these subgroups, then that subgroup is small. That is the point I was trying to make.

DR. WACLAWSKI: I misunderstood. We are not trying to say that it works in any one of these individual subgroups any more or less than it does in the overall analysis which was the study's main objective.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Can I just ask if you have the clinical symptoms and signs data on rheumatoid-factor-negative patients, whether you would put that up, please.

DR. VRATSANOS: Slide 27 from the core, please.

(Slide.)

This is from the trial in methotrexate-inadequate responders with the primary endpoint being the ACR 20 at six months. The rheumatoid-factor-negative group is in the fourth analysis here, consistent efficacy in both positive and negative patients.

DR. FELSON: Thanks.

DR. GIBOFSKY: Anything further on Question No. 1? Anyone else want to comment? Can we go to Question 2? The next sets of questions will really deal with safety. We are asked to evaluate the safety data as identified as well as if we have any other concerns about safety perhaps not brought up by the presentations and, if we do, to what extent there should be studies that should be conducted to further characterize these concerns.

These are statements less than questions, but more serious infections have been observed in

the abatacept-treated group than in the control comparison groups particularly notable for, but not limited to, patients who receive concomitant anti-TNF therapy.

We heard about the infections of special interest which included fungal, viral, in particular, and bacterial infections. The overall infections of special interest were observed in 30 percent greater abatacept-treated patients as compared to control with the majority of the difference in herpes and pneumonia categories. But we are dealing with a patient sample size and exposure duration, as such, that we are still unable to rule out an abatacept-associated increase and the rate of uncommon opportunistic infections.

Comments from the panel? Are these areas of special concern? Dr. Holers?

DR. HOLERS: I think so. I would just like to clarify one point which is that the breakdown of associated use of DMARDs as biologics versus nonbiologics. But I was wondering, it seems that leflunomide stands out in this class of

nonbiologics. I am wondering whether a more appropriate way to break this data out is by mechanism, or known/unknown, and then leflunomide as perhaps something that stands out as perhaps increasing the risk.

I am just wondering what your thoughts are about that. It is a small number, again, but, of all the other DMARDs, this really stands out.

DR. GIBOFSKY: By "your," you mean the agency

DR. HOLERS: Yes; the agency.

DR. GIBOFSKY: Dr. Siegel?

DR. SIEGEL: We didn't break down the nonbiologic DMARDs by mechanism base because, it is my understanding that, for most of the nonbiologic DMARDs, there really is a question about exactly what the mechanism of action is.

It is a great idea. Just, in practice, it might be a little bit hard to do that.

DR. HOLERS: Can I just ask, though, about the leflunomide data, which is on Page 28 of Keith Hull's presentation where 24 percent versus 15

percent. That contrast to the other agents in which there are SAEs at a higher rate. I don't know if that is a meaningful number to you or if it would influence labeling or further studies or not.

DR. SIEGEL: This is the sort of subanalyses that we do to try to understand what the top-line data mean. As you can see, we broke down the safety data based on each individual DMARD, biologic or nonbiologic, that was used concomitantly. We talked about the conclusions for the biologic DMARDs. When you get to the nonbiologic DMARDs, as you mentioned, the only one that seems to stand out is leflunomide.

The difficulty in interpreting this is that, when you look at many different categories, then you have the problem of adjusting for multiple comparisons and you can get an increase by chance alone.

So we were not exactly sure what this meant, if it was spurious or real. So we looked in detail at the adverse events that were seen in patients receiving concomitant leflunomide. Unlike

what we saw with the biologic DMARDs where you saw a clear increase in serious infections, no one adverse event or even category of adverse events stood out with leflunomide which, again, made it more difficult to understand just what this means.

Nonetheless, we would be very interested in hearing what the committee has to say about this and other studies or other information you think might be helpful.

DR. GIBOFSKY: Dr. Holers?

DR. HOLERS: I think I have said everything I know about it. Leflunomide might be a drug that we know a little bit more about its mechanism of action than the rest of these nonbiologics. But your point is well taken. If you didn't see a signal, then I think my concern is addressed.

DR. GIBOFSKY: I would agree. Anyone else? A question for you, Dr. Siegel. Is that language, the last sentence of Question 3, language that is being contemplated to be included in the label or wag your finger at the sponsor?

DR. WALTON: No; we are not presenting any specific labeling language to you in these questions, rather to emphasize these are a category of infections where we have so few observed infections that the confidence interval on the relative risk between the treated and the control group is very broad so that our confidence in the observed data is relatively less than in some of these other categories.

DR. GIBOFSKY: Any comments? Dr. Felson?

DR. FELSON: I am not sure I have a specific comment other than to raise a concern that I think is running through many of our minds about high rates of serious infection in vulnerable people. Older people weren't studied here. Kids weren't studied here. I think I would be real concerned about vulnerable people getting this therapy.

I am real concerned about vulnerable people getting TNF inhibitors, too. I think this has the same sort of gestalt. I am not sure that, despite the pharmacovigilance plans, given the

complexity of care in the real world and the absence of a controlled situation, we are really ever going to know the level of immunosuppression and infection risk that occurs expect, perhaps, with one unique--like tuberculosis, or something like that, where it is a very unique infection that we can enumerate. Otherwise, we are not going to know.

So I think there is a concern here that there is an excess of infection. I am not sure it is any different from TNF inhibitors or anakinra, but that vulnerable infections are going to be at risk. I would love to see data on older people and on people--well, I think that the sponsor's plan to advise against use with biologics is a wonderful idea and I think an appropriate step, at least in that direction.

DR. GIBOFSKY: Let me extend Dr. Felson's comments. I think what you are hearing is the concern about--and I think Dr. Elashoff also alluded to this earlier--the concern about extrapolating from clinical trials where there are

well-defined inclusions and exclusion criteria to clinical practice where you are treating patients, many of whom may not have met the criteria for entry into the clinical trial.

So, to what extent we can extrapolate from clinical trials to clinical practice is always a concern and that level of concern is higher or lower depending upon the number of patients studied, the different categories studied and so on. But that is the natural queasiness that comes out when looking at data from a clinical trial and then scratching one's head and saying, now, how will I use this when the drug comes out.

Dr. Finley?

DR. FINLEY: Dr. Gibofsky, just taking your point a step further in the trial, and it is anticipating the next question, in the malignancies in the lung, I seem to remember this morning's presentation that they went back and the sponsor looked and some of those folks, and, again, thinking about your notion of the controlled environment of a trial, even in that situation,

there were at least two occasions, I think, if memory serves, where they reflected that these people probably had neoplasms that predated their entry into the trial which then bespeaks the notion of the messy ares where we all practice where patients probably wouldn't fit into trials at all because of concomitant medications and not following up and a variety of other things. I think we all have a concern about this very thing.

Then I also wonder about the notion of--and the trials were short enough--the notion of viral infections particularly and their association or predictability in clinical practice with sentinel events for future neoplasms or stuff like that, just things that occur to me as we sit around and discuss this.

DR. GIBOFSKY: Other comments on this theme? Dr. Walton?

DR. WALTON: I would like to have an understanding of--for these areas, as you go through and discuss these questions, for these areas that you have concerns that we don't yet know

everything we might want to, how would you want to see us gain the further information?

The sponsor has proposed certain kinds of pharmacovigilance studies. Are proposals along the lines of what they have made suitable? Would you see other kinds of studies that might be necessary to get an adequate answer. For instance, obviously, observation of patients in clinical practice gives us one kind of information but it can be difficult to draw conclusions with the absence of controlled studies.

But will we be able to manage without that more rigorous form?

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: Dr. Walton, let me just reflect your question back on you. They proposed, if memory serves, the notion of looking at a database that, at least from the prescribing, represents about 2 percent of the population. I would ask, is that, from the agency's perspective, a broad enough cohort when we are thinking about novel therapies or biologics.

I am not sure, as a practicing rheumatologist, I know what the right cut point might be. I am just kind of wondering what, given the division and the agency's experience, what are some guidance in other areas that you might look for that would help us answer that.

DR. WALTON: I think the database size that we have been discussing here today is typical for many of the products that we have brought before the committee for rheumatoid arthritis. So the database we have is not at all atypical for that. It is really, I think, a question of how much concern do the committee members have regarding adverse events that you might wish need further characterization based upon how concerned you might be about the frequency or the seriousness and, ultimately, this will become in comparison--and this will be a question later--but in comparison to the magnitude of the benefits that have been observed.

DR. GIBOFSKY: I think that frames the question. I think we pretty much accepted the

efficacy of the drug. I think the real issue is the issue of safety. I, personally, am very comforted by the pharmacovigilance plan. I think that that will provide us with additional information both in the cohort studies from the insurance-claims base and from the observational safety studies with registries.

I would stress the term "registries," in the plural, because there are several independent registries which, as you know, can be drawn upon for patient enrollment and asking questions about the cohorts.

I think we can't always know what we don't know but I am certainly satisfied that there is a plan to at least monitor intensively and find out what we don't know so that, at various time points, we will be able to understand where we are on this drug.

I am comforted by the data that we have seen to date on the incidence of infections and lymphoma and other malignancies per patient year going out in time, recognizing that they are small

numbers to date. But, as I say, I am very comforted by the plan going forward which I think will give us a information that we need for a new molecular entity.

Dr. Holers?

DR. HOLERS: Just a question, Allan. Do you think the available registries capture the vulnerable populations? I am wondering, in particular, with the V.A., assuming this drug is ultimately used, whether that is a population that is more vulnerable, older and at risk for COPD and whether that is a population that is useful here.

DR. GIBOFSKY: I think you don't want the perfect to be the enemy of the good. In the best world, you would like to have registries for each subpopulation, particularly the older and the vulnerable, the ones with significant comorbidity.

I do think, though, that, by using registries rather than registry in the singular, one begins to nibble away at the issue of differences in populations. So, whether one is looking at the national databank for rheumatic

diseases, or whether one is looking at corona, or whether one is looking at the MedWatch system, I think each of those provide us another walk around the elephant until, ultimately, we are getting to see what we need to.

Dr. Ilowite?

DR. ILOWITE: I just have a quick concern--there were 2000 patients enrolled in controlled studies and the pharmacovigilance plan is for a similar number of 2000 patients, 1000 and 2000 patients, granted for a longer period of time. But, since the question wasn't answered with controlled studies of 2000 patients, I doubt it is really going to come to clarity with the planned number of patients.

I am wondering if the registry should be expanded.

DR. GIBOFSKY: Do you think that the number of patients in the proposed pharmacovigilance program and registry, registries, is sufficient to begin to get a handle on incidence in the particular subgroups that people are

concerned about.

DR. ILOWITE: I am almost willing to defer to Janet for that question because that is almost a pure numbers question. It is now many events do you expect in a population like this and how would you get enough power. I think the sponsor also went into this to detect maybe a doubling of the risk of those events.

I think the problem is one that I think Mike just commented on which is the clinical-trials population is not the same as the clinical population. I would expect a higher event rate in the clinical population and I would want to make sure, also, that those that were vulnerable were represented in these cohorts. I honestly don't know that.

So, what I was going to ask the sponsor is not necessarily the question he was prepared to answer which is does the U.S. Healthcare database include people over age 65? Does it have a Medicare representation to it?

DR. WACLAWSKI: Fortunately, I don't have

to answer that question. Dr. Skovron, who is our global--with the epidemiology program for abatacept can answer that. I also would ask her to clarify the scope of the pharmacovigilance program because it does extend beyond the 1000 or 2000 patients to include a very large observational study. I would like her to clarify that as well.

DR. SKOVRON: I should say, first, that United Healthcare--

DR. ILOWITE: United Healthcare; sorry.

DR. SKOVRON: No problem--that United Healthcare does include a proportion of patients over 65. Some proportion are retired government workers who do not rely on Medicare and some proportion are Medicare. Since this is an infusional drug, it is reimbursed under medical coverage of Medicare.

The other point I want to make is that it is not just one study. United Healthcare is one study that will accrue in proportion to the uptake of abatacept once it is approved because it really has about 2 percent of uses of biologics in this

setting.

We are also undertaking a registry study in which we will enroll 5,000 abatacept initiators and a comparison population as proposed at this time of 15,000 patients, either adding or switching DMARDs or TNF-blocking agents to an existing regimen. Those will be followed for five years after the last patient is enrolled.

DR. GIBOFSKY: Dr. Elashoff?

DR. ELASHOFF: Several comments. One has to do with what I mentioned earlier that there is only 80 percent power to detect relative risks of about 2. We certainly saw with the Cox-2s that it was important to actually be able to do Kaplan-Meier curves rather than just relative risks in looking at things because you don't necessarily expect that the relative risk is going to be constant over time.

With respect to these observational studies, the first one says five years of cohort identification, last enrolled patient followed for two years. So that study doesn't look to be being

done for seven years. The other one enroll 5,000 patients and follow up for five years, so I don't know how early we would expect to get the information from that either.

So I am just pointing out that both of those are pretty long-term and, while 80 percent is an accepted amount of power, still, that is 20 percent chance of missing a relative risk of as large as 2. Also, these kinds of studies are so complex with patients taking--this patient is taking A, B and C in addition and that patient is taking D, E and F, and what do you attribute all these different things to.

So it is very hard to--they are very hard to interpret. So, while we certainly need to do these kinds of things and it can be useful, I think we are still, for a number of years, being pretty much in the dark about how much added risk there might be with these drugs.

DR. GIBOFSKY: One other comment, since you are up there. I notice in Slide 45, the discontinuation rate in that study--I think it is

029--was about 14 percent. So one concern that I would have and ask you to think about going forward, is when you enroll these observational databases, whether it is 5,000 or 15,000, factor in your attrition rate because there will come a point in time at which the number of patients that remain in may be insufficient to give you the kinds of evidence that you may be looking for.

DR. SKOVRON: If I may start with your--we will be tracking discontinuations and we will be following changes in treatment so that those will be factored into the analyses rather than dropping the patients out.

Additionally, we will not wait until the end of study to be examining the frequency of events in the program. We will collect that data, compile the data, annually. We have some formal analyses planned after we have 5,000, 10,000, 15,000, for instance, in the registry, person years on abatacept.

DR. GIBOFSKY: Dr. Felson.

DR. FELSON: I think this is a reassuring

plan and I appreciate your seriousness in developing it. I guess I would say--we have talked about infection, which I think you are getting rates of 2 percent or something like that of serious infection. But your rates of lymphoma, which I think we are concerned about also, for example, which you don't really have enough numbers to look at at this point,I don't think--I don't think anybody would say do you have enough numbers--is 0.08 per hundred person years.

That gives you four lymphomas per 4764 person years, through June 2005, so through a couple of months ago. Now, if you start 5,000 people in a cohort on abatacept, it will be a year before you even get that number, four. And then we go up to five years of follow up and we are dealing with 20 cases of lymphoma.

Now, I hate to go back to Cox-2 inhibitors, but we needed many, many more cases of events to know and have a good sense of an adverse event that was important to us and that we were concerned about than that. I guess I would

encourage the sponsor that, even though, we recognize, that 5,000 patients initiating abatacept is great and god knows when there are going to be thousands and thousands more that, perhaps, even thinking of expanding that number to survey a larger number of people on this treatment for cancer, especially, this is going to give you numbers that are going to be, I think, too small to be definitive.

You are going to wind up--so you get an odds ratio or relative of 20 versus 10 expected. Is that 10 expected--as we now know from your careful work, is that 10 expected from those with RA, those on other biologics, those on other DMARDs? What is the comparison group that gives you that relative risk? It gets confusing and complicated. I think the only way to figure it out is to get bigger numbers and good information on controls and what they are taking.

So I would suggest and urge that 5,000 for lymphoma, for some of the malignancies of concern here. Unfortunately, given the numbers of accrual

of cases, it is sort of small. These are the ironies of this. You need these big numbers to get surveillance.

DR. GIBOFSKY: Dr. Porter

DR. PORTER: I feel like I have entered into a committee for the first time that is on the rebound from the Cox-2 experience which was described to me at lunch. I think the real problem is--and I admit this is the industry perspective, now. The real issue is how safe can you be. If you move down from lymphoma to something else that is even less common, then you are going to need 20,000 patients. If your anxiety is about one more below that, then you need 40,000 patients over ten years.

So I think we have to recognize that this program, which I am hearing, is really, to me, an extraordinary program and probably a sign of the times as we move into trying to make our medicines safer and safer. But don't forget that all of these things add up to the total cost of the drug, too, and we will somehow have to deal with how much

we want to pay for how much safety we are willing--and risk--we are willing to take.

DR. GIBOFSKY: Dr. Felson.

DR. FELSON: Dr. Porter, I guess I agree and disagree. I think that common diseases that we anticipate to be related, likely to be related, given the mechanism of action and our experience in rheumatoid arthritis are ones we need to survey for. Lymphoma is clearly one of those and serious adverse events are also.

With biologics with TNF-alpha inhibitors, we figured the tuberculosis story out without any pharmacovigilance. We figured it out because it was happening--the relative risk of tuberculosis recrudescence was so high that it wasn't very hard to see the signal. I think, for other more uncommon adverse events, we are going to figure it out.

DR. PORTER: It depends on whether you are talking about idiosyncratic reactions which occur 1 in every 20,000 or 30,000 cases--I mean, an anti-epileptic drug, felbamate, was on the market

with 100,000 people before they discovered that 1 out of 20,000 patients had aplastic anemia.

That is a safety level that I am not sure we will ever reach until the science allows us to predict which of these patients is going to get it.

I think that if lymphoma is a common event in this drug because of the mechanism you would suspect, then we shouldn't need all that many patients to figure out whether or not lymphoma is a result of taking this drug.

DR. GIBOFSKY: Dr. Porter, I would just comment that no less a scientific journal than The Wall Street Journal has said to us all here today that, "the drug industry is closely watching today's committee meeting and other meetings this week and next to gauge how tough the agency and its advisors will be on safety questions on several potentially important new medicines."

So the emphasis is clearly on the issue of safety and all of its subanalyses rather than on efficacy. Indeed, the headline of the article that I am reading to you was basically a concession of

efficacy of the drug but a desire that there be a focus on safety

DR. PORTER: Having been involved personally with the development, personally, of hundreds of drugs, you can see the trend toward more safe and more vigilant efforts right here, right now and the company coming forth with five-year plans to follow the safety which you wouldn't have seen five years ago.

So it is obviously a measure of the times that we are seeing this. I also think, however, that we have to recognize that there is a reality of how far we can go with these and make it viable for the company.

DR. GIBOFSKY: Point well taken.

Other comments? Dr. Elashoff?

DR. ELASHOFF: Just a comment that I know, in some instances in the past, and I can't even remember which ones they were, myself, there was concern that a study that was supposed to enroll certain numbers of patients by a certain length of time and be done in a certain time, that was going

very slowly and people were saying, well, it is to the company's interest to have it go slowing so that you don't find out the safety things for a long time.

So I would just encourage us--that there be real efforts on the FDA's part to keep things going along at--and the company's part, I know, trials tend to lag unless you are really out there making a big effort--to try and keep to what is really relatively long time period in terms of safety concerns, although, certainly, it takes a long time to get a lot of patients--I understand--but to keep people to the promised time line.

DR. GIBOFSKY: Dr. Ilowite?

DR. ILOWITE: I think that is very interesting, Dr. Porter's comments. I think that, if we were talking about fatal diseases where there was a tremendous cure rate, tremendous efficacy, that we would put up with less safety. But this is a disease, arguably, that is--well, it is certainly not being cured. I suppose safety takes a more

front seat in this situation where the efficacy is definitely demonstrated, but it is not dramatic.

I don't think it is dramatic. I mean, look at the ACR 70s. So it is hard to talk about safety in the absence of talking about efficacy and how much money we should spend or add to the cost of the drug to get these answers because I think it is going to be the interplay of efficacy and safety that also drives how vigilant we need to be, not just safety.

DR. PORTER: I agree.

DR. GIBOFSKY: Ms. Malone.

MS. MALONE: Just in line with that risk:benefit ratio, if you are someone suffering from the disease and none of these other things are working, you are more apt to take more chances. So I think it is very important for the doctors who are prescribing these drugs to lay this out for the patient. But, again, I think, when you are really hurting, nothing else is working, you see your body deteriorating and all these things happening, you are more likely to take a risk.

I think it is under our purview to have as much safety built into the drug as possible, to know all of that up-front. But, like I say, these are people that have failed traditional therapy, so they are more apt to take more changes.

DR. GIBOFSKY: I think, as we understand, the request is for use of this agent in individuals who have failed at least one DMARD and possibly more. So I think what our patient is reminding us is that, for some people, where this does offer the possibility of assistance, it is a benefit to them and, certainly, an option that may want to be extended to them with the full listing of all of the warts and concerns that we have and may not know enough about.

Is that a fair statement?

MS. MALONE: Yes.

DR. GIBOFSKY: Question 4, I think, has already been addressed in part by Dr. Felson. Does anyone else have any comments about the malignancy issue, both from what we have seen in the human data to date, and any comments on what we heard

about the murine model? Anything further on malignancy that anyone would like to comment on? I think it is obviously a concern, as it is with all biologic agents.

As we heard earlier today, whenever one perturbs the immune system, the law of unintended consequences may come in. So I think we just have to watch carefully. I don't think we can say anything more than what has already been presented.

Hypersensitivity reactions have been observed. I think, in response to my question earlier, the representative from BMS gave a very nice discussion of that as did Dr. Hull. Is that a concern, a particular concern, to anyone on the committee that warrants further discussion? I think we recognize with infusions, as well as with injections, there are going to be these issues as well as with oral preparations.

So I don't think we have seen anything of a magnitude that triggers a particular red flag on this. Is that fair? Does anyone want to comment further?

Perhaps we can talk about the special situations that were identified in the back of the briefing book, namely COPD, diabetes and asthma, I believe, was the third category. Anyone want to tackle that? We didn't really hear much, other than diabetes, discussion this morning about these.

Norm, your thoughts?

DR. ILOWITE: Well, I always have thoughts--it is a problem for me as a pediatrician, I suppose--I certainly always have thoughts about off-label use in children and I certainly appreciate that the sponsor is conducting what I know to be a well-designed trial on children. I am glad enrollment is good.

I have the same concerns about that trial and the numbers of patients being enrolled in other countries as in the adult trials. But it would be nice to do similar pharmacovigilance studies in children who are getting off-label use and follow it for longer periods of time because their exposure is likely to be longer than adults that get the drug starting later in life.

DR. GIBOFSKY: Perhaps, we can get some amplification from the sponsor, in particular, on the CHF issue. That, of course, has been a bugaboo with regard to treatment of patients with the anti-TNFs. We have but one line in our briefing document, under 511.3, that, overall, the frequency of SAEs and discontinuation due to AEs with abatacept and placebo were comparable between the groups.

Can we get a little bit more detail to drill down on on that particular CHF?

DR. MacNEIL: One of the trials that we conducted did have a very small number of patients who had a history of congestive heart failure who entered. There were only nine patients in each group. It really would be hard to draw conclusions from that small sample.

In the overall safety database, if you look at cardiovascular events, there were 5.0 percent of patients in each group who had cardiovascular adverse events. If you looked at specifically congestive heart failure, it was 0.3

percent on abatacept versus 0.6 percent on placebo.

DR. GIBOFSKY: Also, while you are up there, would you chat a little bit more about the higher rates of adverse events in the patients with COPD and diabetes, once again.

DR. MacNEIL: Also, in that same trial, we had patients with a history of obstructive pulmonary disease. In terms of adverse events, there were 27 percent of patients on the abatacept group versus 6 percent who had serious adverse events in that group. There were 54 patients that were in the sample with a 2-to-1 randomization. That was 37 patients on abatacept versus 17 on placebo.

If you look at the overall adverse-event profile, you say more respiratory-type adverse events. I think the numbers were an approximately 20 percent difference. Then, if you look specifically at the serious adverse events, there were three serious adverse events that were pulmonary-related symptoms. There was one of bronchitis and two patients had worsening

obstructive pulmonary disease.

In terms of diabetes, the difference was predominantly in serious adverse events and that difference was related to the musculoskeletal disorders, reports of rheumatoid arthritis, and also in the injuries system-organ class which were falls and fractures.

DR. GIBOFSKY: Do you have any data about the concomitant use in the trials of abatacept in patients who may have been on corticosteroid as well, and whether they had any increased incidence of AEs given the potential propensity of inducing diabetes with corticosteroid?

DR. MacNEIL: Overall, in our studies, about 75 percent of the patients in both treatment groups had received steroids. So there is no overall difference between the two populations in terms of the adverse-event profile and those who received steroids versus those who did not.

DR. GIBOFSKY: Any other questions from the members of the panel? Any other issues of safety that we have not specifically addressed in

the first six parts of the question? Anyone have any other issues you would like to bring up? Dr. Holers?

DR. HOLERS: In the interest of going through this discussion again about what are you looking for and can you find it, I did want to come back just to discuss briefly the issues about unintended consequences of immunosuppression.

I think this drug is a terrific drug for RA. And the safety profile and everything that we have seen really follows very much of what you would anticipate based on what we know about co-stimulation and CTLA4-Ig in models in that there is likely to be a slight increase in infection and risk because T-cells are necessary to wall up bacteria, that viral infections may go up slightly because that is another thing that T-cells do.

The problem comes when you are looking at the issues of development of the immune repertoire in the fetus and the potential effects of CTLA4-Ig and blocking of co-stimulation during fetal development. What, then, happens to the child as

it ages? Is it more likely to develop Type-1 diabetes using as the most likely event, and is the risk of that--first of all, is it understandable, can we study it and should we study it. Do we have enough experience to even know about it? What should we hold the sponsor to? What standards should we hold the sponsor to in a risk that is, perhaps, predicable?

It is not something we would just, like the flood, be surprised about, but it is something that you could predict based on known immunologic concepts--and Dr. Bluestone, who is one of the fathers of co-stimulation, publicly writing about concerns about using co-stimulation in this setting.

So I would like some discussion, I guess, from the FDA, perhaps, from the agency and the rest of the committee, about is this something we should hold the sponsor to or are there other approaches we should be thinking about with regard to this class of drugs, first, of the co-stimulation inhibitors coming through because there will be

more.

DR. GIBOFSKY: Dr. Siegel or Dr. Walt, care to respond?

DR. WALTON: I think, as you have heard, we highlighted some of these theoretical bases of concern that you are bringing out as well. I think, actually, part of the reason for this committee meeting is to hear from you how concerned you are and, if you advise that that is an important question to get further information about, and the nature of the information that you would want us to be obtaining.

We have not made any decisions on the product or what types of further requirements we would see. So we are looking to really hear from all of you in the process of reaching those decisions.

DR. GIBOFSKY: The long-term issues with co-stimulation in 25 words or less, Dr. Holers

DR. HOLERS: I think a reasonable period of time of following children of women who inadvertently used this or advertently used this

drug for five years, or perhaps even upward of ten years, would identify an clinically significant events that occur due to transmission across the placenta. That is my own sense of where we could go with this.

DR. GIBOFSKY: Previously, I saw horizontal nodding of the heads behind you. Now it is all vertical. Is that something that the sponsor is prepared to address in his pharmacovigilance program?

DR. WACLAWSKI: I think in two respects. We have a pregnancy registry this will have in which we will be able to follow not just the gestational period between the post-gestational period in life span for the child. We would actually recommend, even if you become pregnant on the drug and wish to continue it knowing the risks as a class Category B drug that you not consider beast feeding because that would enable additional exposure.

Our experience at Bristol-Myers Squibb, as a research organization in the HIV field, is

somewhat informative on this in that we have made commitments and have followed through on commitments to follow children that were born to women that were exposed to nucleoside therapy as well for developmental issues, not of this nature, sort of was their immune system intact or where they more prone to autoimmune diseases in their childhood era, but to at least follow them for developmental issues.

So that is something we have some experience with as well.

DR. GIBOFSKY: Thank you.

Dr. Felson.

DR. FELSON: I guess, given the theoretical and justifiable concern and the fact that everything else seems to be sort of falling into place in terms of what we would have expected, why would you ever want to treat a pregnant woman with this? There are so many other options available, given the risk that you have described. Why would you even take the chance?

DR. GIBOFSKY: I think, as Dr. Holers said

before, it is the difference between inadvertent and vertent.

DR. FELSON: No; I agree with that. There is obviously going to be an inadvertent exposure occasionally but is there some labeling or some classification that would strongly discourage use--like leflunomide is strongly discouraged. Are there other similar--

DR. GIBOFSKY: Dr. Walton or Dr. Siegel?

DR. WALTON: Certainly, we can put language into the labeling that has a range--in theory goes from a range of no concern at all to extremes of concern. We tend to do that based upon the data that we have, either from our clinical experience or from or preclinical experience.

Again, this is a case where we would certainly be interested in your levels of concern that would help guide us in how to write the language of what you feel would be appropriate levels of concern.

DR. GIBOFSKY: I guess the only comment I would make in response to that with regard to the

preclinical studies is that, of course, they are not in animals with the disease that is under investigation. So it is a somewhat different model. While the data that we heard earlier today about events occurring at three- and 11-fold levels of the drug we are encouraging, these were not in animals with the disease such that one can already deal with a baseline of immune perturbation. I think that would be something of concern.

Certainly, I think Dr. Holers has already outlined for us an area of great concern among his colleagues which is the subsequent development of autoimmune disease or autoimmune manifestations in the offspring of patients. Even were there not to be a commitment to the pregnancy registry, I suspect we would soon see one develop because of the concerns about this occurrence.

Ms. Malone, I think I cut you off in your other questions.

MS. MALONE: That's okay. It was in line with what Dr. Felson said. I think the risk:benefit ratio is just too high to foster, or

even encourage, pregnancy, that it would be more a case of something inadvertent.

My other question was what is the mechanism for reporting to FDA when these registries are indicating something? How soon is FDA told about it or do they report monthly, bimonthly, yearly?

DR. WALTON: When registries of various kinds are set up, we always have a plan of some sort of periodic reporting. Even in the absence of a registry, there is a requirement for annual reporting to the agency. But, more importantly, for events that are serious and unexpected, those the companies do report to the agency on a prompt expedited basis.

It obviously can become follow up to interpret a single event but, for such unexpected and previously unseen events, companies do report to us promptly.

DR. GIBOFSKY: Does that answer your question, Ms. Malone?

MS. MALONE: Yes.

DR. GIBOFSKY: Okay. Dr. Weiss?

DR. WEISS: Just to add onto that. If there are specific events that may not rise to the level of serious and unexpected but ones that are of interest for whatever reason, we can also ask for certain things to be reported on a more frequent basis. So we have a lot of liberty and leeway in terms of what we work out with our sponsors in terms of what we want to see and how we want to see that.

Just to also comment on the pregnancy issue, it is interesting you brought up the issue about discouraging or encouraging whatever use because there is sort of standard boiler-plate language that goes into all of our labels that you probably have already seen. I think the language says something to the effect of, because of the unknowns and potential risk, this should only be used in pregnant women if, clearly--I think it is if clearly needed.

It leaves a lot to people's judgement about whether or not certain therapeutics are

clearly needed. It is very standard language that tends to be recommended if not required by law to be put into these labels.

DR. GIBOFSKY: Thank you. Further discussion? It has been my general experience that a break is needed sooner after lunch than it is after breakfast. So I think what we will do now is take a 15-minute break, come back and discuss Question No. 9 and then go to Question No. 8.

So we will be in recess for 15 minutes and resume at 2:20 by the clock on the wall.

(Break.)

DR. GIBOFSKY: I think we will conclude our break and resume the afternoon session. We are in the home stretch.

As promised, let's begin with Question 9 which is a request to give the agency some additional advice, if you will, on assessing disease activity both in patients who achieve low disease activity as well as patients who have high disease activity and looking at measurements of remission and clinical response.

We heard earlier that, in addition to the ACR responder index, the sponsor also collected data on the percentage of patients achieving low disease activity as assessed by the disease-activity-score-28-defined remission with four variables. Now, since is a composite of tender joints, swollen joints, pain and acute phase reactants, as we know, one can achieve a disease activity score 28, or 44 for that matter, below the criterion for remission but still have multiple tender and/or swollen joints.i

So the question that we are asking to provide some additional advice on is to what extent assessing the proportion of patients achieving low disease activity provide important information of a nature not adequately assessed by analyzing the proportions of patients achieving high levels of improvement such as an ACR 70 or a major clinical response and to give a little insight into our rationale for that discussion.

Dr. Felson, can I ask you to begin the discussion, please.

DR. FELSON: I chair the ACR committee that is reevaluating the definitions of response in rheumatoid arthritis. We have had a lot of discussions about this issue and it was also discussed at some length at the last OMERAC Conference in California.

So we developed, at that time, a definition of low-disease activity. By the way, there are two alternate ways of defining this and the way that we saw here today was the DAS version--there is non-DAS version also--which doesn't necessarily get into the same troubles as the DAS version because you can't get a low disease-activity level in the non-DAS way and have lots of tender and swollen joints. You have to basically have almost none, or one.

DR. GIBOFSKY: Are you referring to measures like the S-DIE and the C-DIE or--

DR. FELSON: No, no. There is a non-DAS version of definition of low disease activity that uses the core-set measures. I honestly don't remember what it is. It is an algorithm of less

than or equal to one tender joint, less than or equal to one swollen joint, et cetera.

The concept here is a valuable one meaning that we not only want patients to improve by a certain amount but we want them to reach a state of low disease activity, or remission, that is clinically appealing to them and to us. After all, if you start off with very, very active disease, you can do a lot better and still have lots of disease activity and be quite disabled and be in pain.

So the idea of getting to a certain point of low disease activity was one that we felt was a very appealing idea. It dovetails and parallels the idea of partial remission in cancer and oncology trials. And that was the model we used.

Having said that, a very important cautionary note which we have discovered as we have analyzed lots of trial data in the ACR effort which is, if you use low-disease activity as primary outcome, a dichotomous primary outcome, in trials, it is just about the worst, least sensitive,

outcome measure in all of the trial data we have looked at. So I would really strongly discourage its use as a primary outcome measure in trials.

It just doesn't work very well. But it is an important clinical--additional sort of adjunctive clinical piece of information about how many patients get to a state that would be desirable for them and for us as their caring physicians.

DR. GIBOFSKY: So, in terms of reaching some kind of activity score or definition that would be more useful, you would favor, then, I take it, the continuous one rather than the dichotomous because of all the problems inherent in it.

DR. FELSON: As I mentioned, we are sort of reevaluating the ACR 20 and I think some folks on this committee are members including the FDA's active involvement. I think we are certainly moving to an ordinal or continuous way of defining response because it looks like it is a much more powerful way of defining response. I think--today, we didn't really see that much because we have an

effective therapy that, basically, shows signal regardless of how we define the outcome. But that is not so commonly the case sometimes.

DR. GIBOFSKY: Dr. Holers? Comments?

DR. HOLERS: I have to plead relative ignorance. Having played a role in getting him to chair that committee, I will have to defer to his--

DR. GIBOFSKY: I would say that was relative smartness rather than relative ignorance.

DR. HOLERS: But I think we certainly want to see no joints involved. That is a very important clinical outcome.

DR. GIBOFSKY: Dr. Elashoff.

DR. ELASHOFF: While I think it is always useful to try to characterize important aspects of what is going on and add information, I don't have any comments on any specifics of this particular measure except to say that whatever its advantages or disadvantages, I would be in favor of keeping the ACR 20 et cetera as major outcome variables in studies so that we can look back and make comparisons with the information we already know

about other drugs because, in any situation where you switch to some new and marvelously better outcome measure, then you no longer have those comparisons and you are in trouble when you want to do a meta-analysis and that sort of thing.

So, irrespective of the sort of intrinsic value of any particular outcome, I would like to argue, from a historical point of view, to keep ones that have been widely used so that you can go on making comparisons of the results of your newer studies with the results of older studies.

DR. GIBOFSKY: Thank you.

Dr. Ilowite?

DR. ILOWITE: We had a consensus conference in pediatrics where remission criteria were developed. I don't deal with the deaths, really, or the ACR 20, 50 and 70 very much. We have our own measures in pediatrics. But it seems almost silly to define a remission as having, even in the most rigorous, stringent definition, as having a tender joint. It says "less than or equal to one tender joint."

It seems to me a remission is no joints that are inflamed, however we define that. So, in some ways, it is not the same thing as what is being done in oncology. So, in pediatrics, we have generated more stringent criteria for remission.

DR. GIBOFSKY: I think what, in part, these measures reflect is our frustration with being able to define when the individual patient has received the best outcome and, also, balanced by the fact that, until several years ago, probably until the advent of methotrexate and then the biologics, we considered ourselves lucky and heroic to get an ACR 20.

Now, we are no longer satisfied with the ACR 20 as the minimum amount. While I agree with Dr. Elashoff that we need to keep these measures so that we can kind of compare trials and particular points, I don't think we need to keep the complacency with a minimum achievement. I think that is why we are all pushing toward remission and trying to get the best possible clinical definition of remission. Whether it is going to be by a

dichotomous variable or by a continuous variable remains to be seen.

The obvious problems with the responder indices, for example, and Ms. Malone certainly understands this better than anyone here, is that if you achieve a 49.9 percent improvement, your are scored as having only achieved a 20 percent improvement in that trial. So we need to do better than that.

Dr. Finley?

DR. FINLEY: Just thinking about what you said and what Dr. Ilowite said, I wonder if we would even think further ahead to think about an ACR 20 being something different, or an ACR 50 or 70, for that matter, being something different in the first two years of their disease onset, the next five years, the next ten years, and thinking, not necessarily about today's discussion but in that context, we are examining patients that had a mean duration of disease of a decade or more.

If we are really trying to achieve remission, we might, as a subspecialty and thinking

about guidance with the FDA and also for industry, we probably need David's leadership and others, some thought about carving up duration of disease in the context of these sets, these datasets, or whatever they might be.

DR. GIBOFSKY: I think that is exactly right. Maybe what the agency needs to be thinking about as the new instruments come out is that the kind of response that would be appropriate as a minimum criteria for one set of disease duration may not be for another.

We are already seeing that, perhaps, we can stratify patients' response by duration of disease and that may require different thresholds for different durations of disease.

Dr. Ilowite.

DR. ILOWITE: I find that it is largely semantic. I think of a remission of if it is achieved and maintained for a certain amount of time that, even after removal of treatment, that the patient will remain with little disease activity. I think that is what the word

"remission" implies. So it would be nice to define this rather than semantically but by outcome over a long-term period of follow up.

DR. GIBOFSKY: Ms. Malone.

MS. MALONE: Just a comment. This is anecdotal, but I have had rheumatoid arthritis for 35 years. During that time, I have had two periods of remission which were--one period was for about two years and another was for about six months.

When you are talking about duration of disease, the disease has had almost a different identify through the course of those 35 years because sometimes the drugs that were available then and the therapies worked for a while. This is not unusual with rheumatoid arthritis. Then they were losing their effectiveness.

Then I would go on to something else and it would work for a while. So there are all like different little packets of duration of the disease. But, all in all, the disease has been sort of like the Ever-Ready Bunny. It is just always there.

Then, after there were the periods of remission or very low disease activity, it would come back with full force. I think that is why it is important to have these additional drugs and to extend hope to people that there is something that will help.

DR. GIBOFSKY: Dr. Siegel?

DR. SIEGEL: I just wanted to clarify a few things. In our question here, we are not taking about remission here. In their rheumatoid arthritis guidance document, there are a number of claims that are described, improvements in signs and symptoms, radiographic progression, major clinical response.

There are two additional claims, complete clinical response and remission. Those are based on the ACR definition of remission, either on anti-rheumatic drugs or if you are off all anti-rheumatic drugs, that would be remission.

So our question here is really not about that. There is a definition of that. But there has been some discussion about reporting something

besides improvement. Since we are not seeing remissions yet with that therapies currently available, what we are asking the committee is if it would be valuable to report something beyond improvement in labels.

It would be helpful to us to hear your thoughts about some specific things, to find remission and, given the particular idiosyncracies of having tender and swollen joints despite a DAS-defined remission, perhaps that plus one of the other more stringent things, but not quite remission because we do have criteria for that.

DR. GIBOFSKY: Dr. Felson.

DR. FELSON: I guess the short answer is, yeah, why not. I wouldn't use the DAS version of it but I think I would use the other version of it which is easier to understand. The DAS works okay but it is a little bit obtuse sometimes. That is why people can find individuals--like they found--like the sponsor found, with several tender joints or swollen joints, who made the criteria for DAS remission. That didn't make any sense.

Norman, I think, just to comment, we were not talking about remission in that discussion. We were talking about low disease activity which--it is in part because, even now, we don't have remission-inducing therapies very often. If we were to define remission as the outcome of interest, I don't think any therapy, even our best therapies, would make it over that threshold.

Low disease activity, you could see that some of these therapies are going to make it over that threshold.

So, yes; I think so. I think the problem, from the practicing physician and lay person's interpretation of the package insert is going to be what is the difference between major clinical response and low disease activity. That is a distinction that we here in this room probably are okay with but if it were later in the afternoon, I am not sure it would be so easy for us.

I think the lay public and the clinician out there may not understand or fathom that difference at all. It may not be a meaningful

difference them. An ACR 70 may be fine for the purposes that we are interested in. By the way, it tends to get very similar results to low disease activity.

DR. GIBOFSKY: It, of course, presupposes that the very strict outcome measurements, whatever they are, that are used in clinical trials, can be used simply in clinical practice. Part of the problem we always face is to what extent the individual using an agent and working with a patient is going to apply strict outcome measurements in clinical practice that are used extensively and exclusively in clinical trials.

Any further comments on this area? I think, obviously, the agency will be very eager to see the results of the ACR 20 Committee working group once it comes out with a report or with OMERAC's collaboration, however it is going to be presented. But, are you comfortable with what we have said to this point? Dr. Walton, were you reaching for a microphone?

DR. WALTON: No. I think we have heard

some good conversation. It has been important to hear the comments regarding the goals that should be looked for as well as the concerns about the difficulty in clearly distinguishing within labeling between some of these different measures.

Thank you.

DR. GIBOFSKY: Is there any further discussion on any areas, any further request for information from the sponsor or the agency, from any member of the panel about anything that has been brought before us today?

Hearing not, I guess we will go right to the money question which is Question No. 8. In view of all the data available for safety and efficacy of abatacept, do the benefits outweigh the known and potential risks?

Let's discuss it, if we have further discussion from the panel, and then let's vote. Dr. Porter, we would value your participation in the discussion but I am reminded that, for today's proceedings, your vote is so precious that it can't be given today.

Dr. Holers.

DR. HOLERS: Just to reflect, I think, the conversation that we have had today which is really the efficacy of this compound is quite well established. I think there is no real question about the and I think we have tried to find the right bar or the right level of safety oversight. And I think we have done a pretty good job of that today so far.

But my sense is that the benefits certainly do outweigh the known and potential risks of this drug.

DR. GIBOFSKY: I would like to hear a brief comment from everyone and then we will take a vote, yea or nay.

Ms. Malone, your comments?

MS. MALONE: I would agree, but I also think it is very important to let the patient know what the risks are to be sure there is that patient education prior to the prescribing of this drug and to let them know that nothing is ever 100 percent safe.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I agree with the previous comments including Dr. Holers. I think there is clear-cut efficacy and the safety profile seems like the other TNF-inhibitors that we now know reasonably well. I think that I would be in favor of saying this has greater efficacy than its problems with safety and toxicity.

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: I would concur with my peers that have spoken thus far. I would also recognize that not only are we talking about a new class of agents but, given the dialogue with regard to pharmacovigilance in collaboration, we may be talking about new day as far as collaboration between the agency and industry which is very encouraging for patients.

DR. GIBOFSKY: Dr. Ilowite?

DR. ILOWITE: I agree with everything that has been said by the panel. I have learned something new today about potential neonatal or young childhood complications of this drug and

would encourage characterizing the fetuses and babies as best possible even with regards to outcomes that might not be attributable right now to autoimmunity.

I mean, 30 years ago, we didn't know anything about neonatal lupus or the current miscarriages from phospholipid antibodies. So just characterizing the babies as well as possible without any preconceived--certainly we could look for diabetes and other autoimmunity disease, but just to characterize them well.

DR. GIBOFSKY: Dr. Elashoff?

DR. ELASHOFF: It does seem to be effective with the caveat about the radiographic progression. I would sort of change this business of known and potential risks because I think potential risks are always very high. But, with the evidence, we can currently see about risk rates, it seems consistent with other drugs.

DR. GIBOFSKY: Dr. Porter, I value your input before we go to a formal vote

DR. PORTER: Thank you very much. I think

the panel has done a marvelous job of extracting all of the discussion issues about this drug. I think they have come to the right conclusion. I think that it is fair to give drugs to patients if they know the risks. I have watched the committees deny drugs to patients because they are afraid of the doctors and the patients not fully understanding the risks.

I think that the pharmacovigilance plan, and I regret to say for my colleagues in the industry is probably going to approach the standard and it is going to be more expensive and it is going to make the drugs more expensive. So I am very much in favor of what you are doing.

DR. GIBOFSKY: I will take the last word just to say briefly that I concur with all the comments. I think the efficacy is quite exciting. I think it is quite exciting, as well, the pharmacovigilance program is being offered up to us rather than being mandated to them. I agree with you that this is, perhaps, an excellent example of what could be done, what should be done, and look

forward to seeing what will be done with it as well.

With that in mind, are you all ready for the vote? Dr. Elashoff?

DR. ELASHOFF: I had one comment which comes from the Cox-2 meeting. Basically, the sponsor said that they were not going to do any direct-to-patient advertising for one year. I think that was one of the strongest things from the Cox meeting is that many people were distressed by having direct-to-patient advertising at all for some of these things. That is something we haven't discussed here, but I just wanted to bring that up as an issue.

DR. GIBOFSKY: Thank you.

Okay, then. Let's vote. Again, I will start from my right. Dr. Elashoff. The question is, does the safety and efficacy of abatacept and benefits outweigh the known and potential risks. If you vote yes, you are saying that the safety and efficacy outweighs the known and potential risks. If you vote no, you are saying that the known and

potential risks outweigh the safety and efficacy.

DR. ELASHOFF: I will say yes. But I am going to stick to the so-far observed risk.

DR. GIBOFSKY: Dr. Ilowite?

DR. ILOWITE: Yes.

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: Yes.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Yes.

MS. MALONE: Yes.

DR. GIBOFSKY: Dr. Holers?

DR. HOLERS: Yes.

DR. GIBOFSKY: Oh, what the heck. Let's make it unanimous. I say yes as well. Thank you.

Is there any further business to come before this committee this afternoon? Dr. Siegel? Dr. Walton? Dr. Weiss? Anything? No.

DR. WEISS: Just to thank everybody for their thorough discussion.

DR. GIBOFSKY: Thank you. Before the committee bolts, let me take care of one housekeeping measure. We are going to be polled in

the very near future for dates for our next meeting which will likely be in January or early February, I am told. Hopefully, once you get the polling e-mail, please respond to it so that the next meeting can be set up and we can have another go at doing good work.

Thank you all very much for your participation.

(Whereupon, at 2:43 p.m., the meeting was adjourned.)

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