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ARTHRITIS ADVISORY COMMITTEE

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ATTENDEES (Continued)

ALSO PRESENT:

MARY ARMITAGE
REGINA VANDERVORT

C O N T E N T S

BLA-99-1234, REMICADE (infliximab) - Centocor

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PROCEEDINGS

(8:05 a.m.)

DR. SIMON: Good morning. I would like to call this Arthritis Advisory Committee meeting to order.

We first are going to go around the table and introduce the members of the committee today. I'd like to start over here on the left.

DR. WINALSKI: Carl Winalski, Brigham and Womens Hospital.

DR. SCHWEITZER: Mark Schweitzer, Jefferson Medical College, Jefferson University Hospital.

DR. KATONA: Ildy Katona, the Uniformed Services University.

DR. WOFSY: David Wofsy, University of California, San Francisco.

DR. ELASHOFF: Janet Elashoff, Cedars-Sinai and UCLA.

DR. WHITE: Barbara White, University of Maryland and Baltimore VA.

DR. SIMON: I'm Lee Simon. I'm a rheumatologist. I'm from Harvard Medical School and the Beth Israel Deaconess Medical Center, and I'm the acting Chair today.

MS. REEDY: Kathleen Reedy, Executive Secretary of this committee for the Food and Drug Administration.

DR. FIRESTEIN: Gary Firestein, University of California, San Diego.

MS. MALONE: Leona Malone, consumer representative.

DR. MILLS: George Mills, Center for Biologics, FDA.

DR. MATTHEWS: Barbara Matthews, Center for Biologics, FDA.

DR. SCHWIETERMAN: Bill Schwieterman, supervisory medical officer, FDA.

DR. WEISS: Karen Weiss, Director of the Division of Clinical Trial Design and Analysis of the FDA.

DR. SIMON: Frank, would you step in?

DR. PUCINO: Frank Pucino, National Institutes of Health, Pharmacy Department.

DR. SIMON: And, Yvonne, would you step in?

DR. SHERRER: Yvonne Sherrer, advisory committee.

DR. SIMON: Thank you all.

I'd like to have Kathleen read the waivers and other information.

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

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

Dr. Steven Abramson is excluded from participating in today's discussion and vote concerning Remicade. Further, in accordance with 18 United States Code, section 208(b)(3), full waivers have been granted to Drs. Lee Simon, Gary Firestein, and Yvonne Sherrer.

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 addition, we would also like to disclose for the record that Drs. Lee Simon and Gary Firestein have interests which do not constitute financial interests within the meaning of 18 United States Code, section 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Simon and Firestein may participate fully

in today's discussion and vote concerning Remicade.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Dr. Schweitzer would like to disclose for the record that he is a co-investigator on an Immunex product and receives nominal consulting fees from Immunex. Dr. Wofsy would like to disclose for the record that he was a co-investigator at one site of a multicenter trial of Enbrel, sponsored by Immunex. The study ended one year ago. However, they are still following a few patients in an open-label extension study. Dr. Wofsy does not receive any salary support from the sponsor.

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

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

DR. SIMON: Thank you, Kathleen.

We are going to have a very chock full morning,

and therefore we are going to get started. I want to remind everyone to jot down questions that they might have. We won't have a lot of time for asking a lot of in-depth questions immediately after the initial presentations. However, we may need to look at some issues of clarification. Since there's not a lot of time, we want to be sure that we are very efficient about doing that. So, without further ado, I would like to open up with the Centocor presentation.

MR. PAGE: Thank you, Dr. Simon.

Dr. Simon, committee members, I am Martin Page, Vice President of Regulatory Affairs for Centocor. On behalf of Centocor, may I express appreciation for this opportunity to present data on Remicade, or infliximab, for the treatment of rheumatoid arthritis.

Infliximab is a chimeric monoclonal antibody that is specifically directed against human tumor necrosis factor alpha.

Rheumatoid arthritis is a severely debilitating disease. Many therapies treat only the signs and symptoms, but products are now available which slow the progression of structural damage. However, there is still an unmet medical need for products to prevent structural damage and improve physical function, particularly in patients with active disease despite use of DMARD therapies, for example,

those with an inadequate response to methotrexate.

The data presented today from the ATTRACT trial will show that treatment with Remicade, in combination with methotrexate, significantly prevents structural damage with respect to erosions and joint space narrowing in patients with an inadequate response to methotrexate.

Remicade also improves physical function measured by validated instruments such as the Health Assessment Questionnaire, or HAC, and the physical components of the SF-36, a quality of life questionnaire.

Remicade was first approved in 1998 for the short-term treatment of signs and symptoms of moderately to severely active Crohn's disease, as well as reducing the number of draining enterocutaneous fistulas in fistulizing Crohn's disease. Remicade is the first and only product approved for fistulizing disease.

In November 1999, based principally on the 30-week results from the ATTRACT trial, Remicade in combination with methotrexate was approved for the reduction of signs and symptoms in rheumatoid arthritis patients who have had an inadequate response to methotrexate. The currently approved dose for rheumatoid arthritis is 3 milligrams per kilogram as an intravenous infusion, followed with additional 3 milligrams per kilogram doses at 2 and 6 weeks after the first infusion,

then every 8 weeks thereafter.

The ATTRACT trial is a 2-year, placebo-controlled, double-blind randomized study of repeated infliximab treatment with concomitant methotrexate therapy in patients with an inadequate response to methotrexate.

The FDA guidance to industry defines several claims for the treatment of rheumatoid arthritis, one of which is prevention of structural damage. Included in the acceptable outcome measures to support a prevention of structural damage claim is evaluation of x-ray progression over at least 1 year, using a validated radiographic index.

The ATTRACT trial design and primary endpoints were developed and agreed with the FDA to comply with the guidance document and provide the pivotal data to support the proposed indications. Primary endpoints were predefined for treatment of signs and symptoms at 30 weeks, prevention of structural damage at 54 weeks, and improvement in physical function at 102 weeks. However, all three endpoints were evaluated at all three time points.

The trial has been completed, and the 102-week results are now available. They have been shared with the FDA but have not yet been submitted for full evaluation. The main focus of today's presentation will be the 54-week signs and symptoms, radiographic and physical function

results of the ATTRACT trial, although the top line 102-week results will be shown and confirm that benefits observed at 54 weeks are sustained.

Since the ATTRACT trial met the primary 54-week endpoint, we are requesting that the Remicade indication be expanded to include the prevention of structural damage, including both erosions and joint space narrowing, and improvement in physical function.

Following this introduction, our agenda consists of four presentations. Professor Ravinder Maini from the Kennedy Institute of Rheumatology in London, England, will present the scientific rationale and clinical pharmacology of Remicade. Professor Maini has done much of the initial research to establish the utility of anti-TNF therapy in rheumatoid arthritis.

The efficacy and safety results will be described by Dr. Gregory Harriman, Senior Director, Immunology Clinical Research for Centocor.

Dr. Desiree van der Heijde, Professor of Rheumatology at the University Hospital at Maastricht in the Netherlands, will discuss the significance of the radiographic results. Dr. van der Heijde developed the van der Heijde modified Sharp scoring method used for the radiographic assessments in this trial and is also the Chairperson of the OMERACT Imaging Group.

Finally, Dr. William St. Clair, Associate Professor of Medicine, Division of Rheumatology and Immunology at Duke University School of Medicine in Durham, North Carolina, will provide an overall clinical perspective on the use of infliximab in rheumatoid arthritis. Dr. St. Clair has considerable clinical experience with Remicade and was a member of the steering committee for the ATTRACT trial.

The following consultants, listed in alphabetical order, are also present to assist us and answer your questions as necessary. They are Drs. Paul Emery, John Sharp, and Frederick Wolfe.

May I now introduce Professor Ravinder Maini to present the scientific rationale and clinical pharmacology.

DR. MAINI: Thank you, Martin, and thank you, members of the Arthritis Advisory Committee and the FDA.

The purpose of this presentation is to provide you with recently obtained preclinical evidence that Remicade can prevent and even potentially reverse structural damage in both bone and cartilage. In addition, pharmacodynamic data from clinical trials from our institute, carried out since the introduction of this treatment in 1992, has provided extensive evidence that Remicade down-regulates cells, cytokines, and chemokines that mediate inflammation and joint destruction and thus

can prevent structural damage in patients with active rheumatoid arthritis.

This figure depicts the structural components of a normal joint on the left, and shown on the right are the key pathologic features of synovitis and pannus formation resulting in bone erosion and cartilage degradation in rheumatoid arthritis.

Both preclinical and clinical evidence has been provided that TNF is the pivotal cytokine that modulates and potentiates disease progression in patients with rheumatoid disease. At the cellular level, TNF is critically involved in recruitment of immune and inflammatory cells into the joint. TNF is also at the apex of a complex cascade that induces synovitis and pannus formation and drives osteoclasts, synoviocytes, and chondrocytes, as well as other cell types, including polymorphs and macrophages, and results in both resorption, joint inflammation, and cartilage degradation. The clinical manifestations of these are bone erosion, pain and joint inflammation, and joint space narrowing.

Since TNF plays a central role in the pathogenesis of rheumatoid disease, neutralizing TNF would be expected to provide profound therapeutic benefit to patients. To this end, Centocor has developed the chimeric monoclonal antibody called Remicade, or infliximab. This

antibody was genetically constructed using the variable region of a murine antibody specific for human TNF alpha that was combined with the constant domains of the human IgG1 antibody. Remicade binds with high affinity to TNF alpha and neutralizes its effects.

Because it is a monoclonal antibody, Remicade has certain unique features that distinguish it from TNF alpha receptor constructs. Remicade neutralizes only TNF alpha and does not bind lymphotoxin alpha, a pro-inflammatory cytokine that is not shown to be important in the pathogenesis of rheumatoid disease, but that may be important for immune defense.

Remicade forms highly stable complexes with TNF alpha, such that once TNF is bound, it does not dissociate and regain biologic activity.

Remicade is also capable of selectively lysing only activated cells producing TNF alpha, a property that may explain the rapid, profound, and durable effects observed in chronic diseases such as rheumatoid arthritis and Crohn's disease.

Dr. Harriman will shortly be presenting clinical data that Remicade can prevent structural damage in humans. We also have preclinical evidence that infliximab can prevent and even reverse the structural damage resulting from TNF expression in a widely accepted

mouse model of rheumatoid arthritis.

The Tg197 transgenic mouse constitutively expresses TNF alpha and consequently develops synovitis, bone erosion, and cartilage degradation very much like that observed in rheumatoid arthritis.

In this study, arthritic signs were allowed to progress until at least two paws of these mice exhibited distortion of the paw and ankle. Saline or the fully murine version of infliximab was administered weekly for up to 16 weeks. The paws were visually scored every week, and groups of mice were sacrificed at 0, 6, and 16 weeks, and the paws were then subjected to a blinded histological examination. The disease in the saline treatment group was so severe that the mice were sacrificed for ethical reasons between 6 and 9 weeks and were, therefore, included in the 6-week analysis.

As shown clearly in this figure, the mean arthritic score which measures the swelling and distortion of the joints increased over time for animals treated with saline for 6 weeks as shown in red. However, animals that received murine infliximab exhibited greatly reduced arthritic scores as compared with the baseline score and the decline in score continued with prolonged treatment for 6 weeks as shown in blue or 16 weeks as shown in yellow.

To examine the effect of infliximab more

closely, a variety of histological features were evaluated from the joints of these animals, including synovitis, bone erosions, and cartilage damage. The animals treated with saline for 6 weeks, shown by the red bar, demonstrated an increase in synovitis histological score over that observed for the baseline group of animals, shown by the green bar. You will recall that these animals already had significant disease, indicating that without intervention the disease continued to progress. However, the joints from animals treated with infliximab for 6 or 16 weeks demonstrated nearly complete reversal of the synovial inflammation observed at the baseline assessment.

A similar pattern was observed when bone erosion was assessed histologically. Infliximab treatment for 6 or 16 weeks demonstrated a dramatic decrease in bone erosion score relative to both the baseline and the saline-treated animals.

Infliximab treatment also reversed cartilage damage as shown in this slide. In this study, infliximab not only prevented disease progression, but also allowed synovium and damaged bone and cartilage to revert to an essentially normal architecture.

Representative joint sections, stained by hematoxylin and eosin, illustrate the effects of infliximab treatment and reverse the structural damage. Sections from

joints of animals from the baseline of established disease, 6-week saline and 6-week infliximab treatment are shown in the left, middle, and right-hand panel. In the left panel, a large number of purple staining infiltrating cells into the pannus is easily discernible as shown by the big black arrow, and cartilage degradation and bone erosion are also observed, as shown by the smaller arrows.

In the middle panel, markedly increased inflammatory cell infiltration, bone erosion, and cartilage degradation are observed in the joint of an animal treated with saline for 6 weeks.

In contrast, in the right-hand panel, a previously distorted joint showed no visible cartilage or bone erosion, and nearly all signs of inflammatory cell infiltration had disappeared following 6 weeks of treatment with murine infliximab. The arrowhead demonstrates the region of pannus formation and cartilage.

Cartilage damage as further examined by toluidine blue staining of healthy cartilage of serial sections from the same animals as shown in the previous slide. Only a little dark blue staining for proteoglycan in the cartilage was present in the joint of the baseline animal, as shown by this arrow. Almost no proteoglycan was observed in the animal treated with saline for 6 weeks as shown in the middle panel. You see the cartilage depleted

of matrix. Healthy cartilage matrix exhibiting intense blue staining was shown in animals treated with infliximab for 6 weeks. The animals treated with infliximab for 16 weeks showed further improvement in synovitis, bone erosion, and cartilage degradation, and these animals have essentially normal cartilage and bone architecture.

The Tg197 mouse study demonstrated that it is possible to prevent and even reverse structural damage in this animal model. Pharmacodynamic data from clinical trials has verified that Remicade can also prevent the disease process from progressing that causes bone and cartilage destruction in patients with the rheumatoid disease.

We first assessed the effects of Remicade treatment upon a variety of mediators of cell recruitment. Synovial biopsies obtained before and after Remicade administration were evaluated histologically for the presence of the adhesion molecule E-selectin and chemokines, monocyte chemotactic protein, MCP-1, and interleukin-8. Remicade treatment significantly reduced all these three mediators of cell recruitment. In addition, it had similar effects on ICAM-1 and VCAM.

These photographs further illustrate the presence of MCP-1, E-selectin, and IL-8 in the top panel before Remicade treatment and their reduction or absence

after Remicade. These were taken 4 weeks after treatment.

Pannus growth is dependent on neovascularization which is regulated, at least in part, by the potent vascular endothelial growth factor, VEGF. Plasma VEGF concentrations are significantly reduced following administration of Remicade and these results are sustained through at least 4 weeks following a single infusion, as you can see here, a dose-dependent effect. High dose, low dose of Remicade.

A reduction in the mediators of cell recruitment results in a decreased number of immune and inflammatory cells recruited into the joint. Extensive infiltration of CD3 positive cells before treatment is reduced after Remicade. Following Remicade treatment, the decrease we believe would indicate that activated T-cells that might be expressing RANK ligand and therefore inducing RANK interactions on osteoclasts would be significantly decreased.

The reduction in recruitment of inflammatory cells to joints following Remicade is also demonstrated in this study. A patient was administered Indium 111-radiolabeled granulocytes, and the infiltration of these cells into the knees and hands is shown in the top left- and right-hand panels, respectively. Two weeks following a single Remicade infusion, radiolabeled granulocytes were

again administered, and the decreased trafficking of these cells to the same joints is readily visible. These results provide a global perspective of the effect of Remicade upon cellular retention and infiltration into the joint.

Remicade also reduces mediators of cartilage degradation, and though we have not measured these in the joint, we have measured the proenzymes in blood. We believe MMP-1 and MMP-3 mediate cartilage destruction, and similar to the profile observed for VEGF, we see a decrease in pro-MMP-1 and pro-MMP-3 in the serum of the patients treated with Remicade. There is a dose-response effect; high dose, low dose, placebo-treated patients.

This probably reflects turnover of these proteinases in the joints and the down-regulation of these proteinases might be expected to reduce cartilage degradation in rheumatoid disease, thus leading to prevention of joint space narrowing, as Dr. Harriman will shortly present from the ATTRACT trial.

To summarize the results from the clinical and preclinical studies, Remicade first binds to TNF and neutralizes its effects upon cell recruitment and infiltration into the synovium and pannus formation and then down-regulates the inflammatory and destructive effects of osteoclasts, synoviocytes, and chondrocytes. Thus, by neutralizing the effect of TNF upon all these cell

types, Remicade can improve not only joint pain and inflammation but also cause prevention of joint space narrowing and bone erosion.

In summary, it is well known that TNF mediates joint destruction in rheumatoid arthritis by causing synovitis, pannus formation, bone erosion, and cartilage degradation. Infliximab has been demonstrated to prevent and reverse the damage to bone and cartilage in a mouse model and Remicade treatment in patients, using a variety of pharmacodynamic measurements, appears to reduce mediators of joint destruction that are associated with synovitis, pannus formation, bone erosion, and cartilage degradation in patients with active disease.

I would now like to introduce Greg Harriman who will review the radiographic and clinical data from the ATTRACT trial and summarize recent post-marketing data from patients with rheumatoid arthritis. Greg.

DR. HARRIMAN: Thank you, Professor Maini. Good morning, Mr. Chairman and members of the committee and FDA colleagues.

I am pleased this morning to present the efficacy and safety results from clinical trials with Remicade demonstrating that Remicade is safe and effective for the treatment of patients with rheumatoid arthritis. These results provide compelling evidence that Remicade, in

combination with methotrexate, at a dose of 3 milligrams per kilograms every 8 weeks, as well as higher doses, prevents structural damage, both bone erosions and joint space narrowing, not only through 1 year but, as you will see, through 2 years. These results are supported by evidence of sustained clinical benefit with respect to reduction in signs and symptoms through 54 weeks, as well as evidence of improvement in physical function.

Finally, the safety experience with Remicade, not only from the ATTRACT trial, but other clinical trials, long-term safety follow-up and post-marketing experience, demonstrate that Remicade is safe and well-tolerated.

The FDA guidance document for treatment of rheumatoid arthritis is intended to provide guidance regarding appropriate outcome measures to support new claims for the treatment of rheumatoid arthritis. This document provides the following examples of outcome measures that could be used to support a claim for prevention of structural damage: slowing x-ray progression, using either the Larsen, the modified Sharp, or another validated radiographic index; prevention of new x-ray erosions by maintaining an erosion-free state or preventing new erosions; or other measurement tools, such as MRI. With this in mind, the primary radiographic endpoint in the ATTRACT trial for prevention of structural

damage -- that is, the change from baseline to 54 weeks in the van der Heijde modified Sharp score -- was developed following discussions with and concurrence by the FDA.

I'd like to take a moment to review with you what we mean by prevention of structural damage.

In trying to understand what underlies the structural damage observed in patients with rheumatoid arthritis, Fred Wolfe and John Sharp followed a cohort of 256 rheumatoid arthritis patients longitudinally for up to 19 years. An important finding of this study, as shown on this figure, was that both erosions and joint space narrowing made substantial contributions to the progressive joint damage seen in these patients over that period of time. Therefore, preventing this continued progression of erosions and joint space narrowing is what we felt was important when we designed the ATTRACT trial. Let me show you what I mean on the next slide.

We believe an agent capable of preventing progression of structural damage had to go beyond slowing or retarding progression to get as close as possible to preventing any progression in as many patients as possible. What I would like to do now is show you data from the ATTRACT trial that demonstrates Remicade was able to achieve this objective in a substantial portion of patients inadequately responding to methotrexate.

The ATTRACT study was a phase III trial with the anti-TNF alpha chimeric monoclonal antibody infliximab, or Remicade, in combination with methotrexate, for the treatment of active rheumatoid arthritis in patients with an inadequate clinical response to methotrexate.

ATTRACT was an international, multicenter study which included 34 sites in the U.S., Canada, and Europe. It was a randomized, double-blind, placebo-controlled study which examined four Remicade dose regimens in combination with methotrexate compared to placebo plus methotrexate. All patients in this trial, including patients receiving placebo infusions, continued on stable, concomitant doses of methotrexate during the trial.

Three co-primary endpoints were prospectively defined and were agreed with by the FDA. These endpoints were designed to assess outcomes to support claims for improvement in signs and symptoms, prevention of structural damage, and improvement in physical function or disability.

The co-chairmen of the study were Tiny Maini and Peter Lipsky. The study was overseen by a steering committee consisting of the two study chairman, along with Feri Breedveld, Dan Furst, Joachim Kalden, Josef Smolen, Bill St. Clair, and Michael Weisman.

The safety monitoring committee was chaired by David Felson and contained two other members, another

rheumatologist, Frank Wolheim, and a statistician, Charles Goldsmith.

Radiographic scoring was supervised by Desiree van der Heijde.

Laboratory tests were performed by the central laboratories, BARC and Mayo, while radiographic imaging and the presentation system used by the radiographic readers was provided by Bioimaging Technologies.

The ATTRACT study was intended to study patients with aggressive disease which was inadequately responding to methotrexate. Patients had active rheumatoid arthritis despite treatment with methotrexate, defined as at least six swollen and tender joints and at least two of the following: morning stiffness of 45 minutes or more, erythrocyte sedimentation rate of a minimum of 28 millimeters per hour, or C-reactive protein of at least 2 milligrams per deciliter. All patients had to have been treated with methotrexate for at least 3 months and at a minimum stable dose of 12.5 milligrams per week for at least 4 weeks at the time of study entry. Patients had to have discontinued other DMARDs at least 4 weeks prior to screening, and no other concomitant DMARDs were allowed during the trial. Patients were, however, permitted to receive stable low-dose corticosteroids at less than or equal to 10 milligrams per day and nonsteroidal anti-

inflammatory drugs.

The ATTRACT trial included 428 patients randomized equally to five treatment groups. Again, all patients received concomitant methotrexate during the study. There were four Remicade treatment groups which included two doses, 3 milligrams per kilogram or 10 milligrams per kilogram, and two infusion schedules, every 4 weeks or every 8 weeks. Please note that the color codes for the treatment groups on this slide are used on subsequent slides to facilitate identification of the treatment groups. Remicade infusions were administered at 0, 2, and 6 weeks, followed by every 4 or 8 weeks thereafter. The trial was blinded by having the methotrexate group receive placebo infusions. Patients receiving the every 8-week infusions of Remicade received placebo infusions at the 4-week interim visits. Regardless of whether patients continued on study treatment, all patients were to return for efficacy and safety measurements at 30, 50, and 102 weeks.

Three co-primary endpoints were sequentially assessed in the study. Clinical response defined as an ACR20 response was assessed at 30 weeks. Prevention of structural damage was assessed by determining the change from baseline in the van der Heijde modified Sharp score at 54 weeks. An improvement in physical function was assessed

by determining the change from baseline in the Health Assessment Questionnaire, or HAQ, through 102 weeks with no worsening in quality of life as measured by the SF-36.

Primary endpoints were assessed as secondary endpoints at other time points in the trial.

Again, the primary endpoint at 54 weeks -- that is, the change from baseline in van der Heijde modified Sharp score -- was designed and intended to support a claim for prevention of structural damage, as defined in the FDA guidance document.

The radiographic results in this trial were assessed using the van der Heijde modified Sharp score, a validated, well-established, and widely accepted method. Two experienced readers trained by Professor van der Heijde evaluated all patients' films, which were digitized and presented on high resolution monitors. These readers were blinded as to patients' treatment assignment and film sequence. Each patient's films at baseline, 30 weeks, and 54 weeks were read independently by each reader as a set.

The van der Heijde method used in this study scored 44 joints in the hands and feet for erosions and 40 joints in the hands and feet for joint space narrowing. The erosion and joint space narrowing summary scores are the sums of individual joint scores. The total van der Heijde score represents the sum of the erosion and joint

space narrowing summary scores. Higher scores indicate more damage. The final patient score is the average of the two readers' total van der Heijde scores.

As required by the protocol, all patients were to have x-rays taken at baseline and 54 weeks regardless of whether they continued on study treatment through 54 weeks. Overall compliance was good. 88 percent of patients had radiographs taken at both baseline and 54 weeks and 82 percent of patients were included in the primary endpoint analysis. The principle reasons for exclusion from this analysis were incomplete sets of x-rays or views in 15 percent of patients and insufficient number of evaluable joints due to prior surgery or image quality in 3 percent of patients.

The statistical methods applied in this trial used an overall test for treatment effect comparing the five treatment groups. Pair-wise comparisons were made between the placebo plus methotrexate group and each of the Remicade with methotrexate groups. All hypothesis testing was two-sided and used intention-to-treat principles. The overall type 1 error rate for the three co-primary endpoints was controlled at the .05 level.

As indicated previously, the primary endpoint for prevention of structural damage was the change from baseline to week 54 in the van der Heijde modified Sharp

score. The primary analysis compared treatment groups using non-parametric analysis of variance at an alpha level of 0.025 to control for multiple comparisons. All patients with evaluable sets of x-rays at week 0 and 54 were included in the analysis according to their randomized treatment group.

The study population enrolled in ATTRACT was well balanced with respect to baseline characteristics and consisted of patients with active rheumatoid arthritis inadequately responding to methotrexate.

This slide and the next show the baseline patient characteristics for all patients in the study. This was a typical population of patients with active rheumatoid arthritis, having a median age of 54 years, female predominance, and a majority of patients with positive rheumatoid factor. Patients had been on a median of three prior DMARDs, including methotrexate, with a range of 2 to 8. Patients were on therapeutic doses of methotrexate prior to entry with a median dose of 15 milligrams per week.

Despite being on therapeutic doses of methotrexate at baseline, patients had active disease. They had a median of 20 swollen and 31 tender joints, as well as a median CRP of 2.6 milligrams per deciliter. They also had substantial disability at study entry, indicated

by a median HAQ score of 1.8.

The baseline patient characteristics indicate that this study included a broad patient population with respect to disease duration, functional class, and baseline radiographic scores. Thus, while many patients in the trial had longstanding disease, as indicated by a median disease duration of 8.4 years, there was a broad range of disease duration from 6 months to almost 50 years, and approximately one-fifth had a disease duration of 3 years or less.

49 percent of the patients had severe prior damage caused by rheumatoid arthritis being in functional class III or IV. However, the trial also included many patients with less advanced disease with half being in functional class I or II.

At study entry, patients had a median baseline radiographic score of 51. However, again, there was a broad range from no damage with a baseline score of 0 to severe damage with a baseline score of 382.

Finally, the median annual rate of radiographic progression in patients prior to study entry was 7.2 van der Heijde modified Sharp score units.

This slide shows reasons why patients discontinued study treatment, that is, study infusions by treatment group. As shown, 50 percent of patients in the

placebo group discontinued study treatment infusions through 54 weeks. Fewer patients in the Remicade groups discontinued study treatment. The primary reason for discontinuing study treatment was lack or loss of efficacy, with 36 percent of placebo patients discontinuing treatment for this reason. No differences were observed between treatment groups in study treatment discontinuation due to adverse events.

It is important to note that regardless of whether patients were continuing to receive study treatment infusions, all patients were to return for clinical and radiographic assessments at 30, 54, and 102 weeks.

In fact, a large proportion of patients continued on study and returned for 54-week assessments. Thus, 78 percent of patients in the placebo group and 90 percent or more of patients in the Remicade groups returned for the 54-week assessment. Although a number of patients discontinued study treatment infusions, the vast majority of patients continued treatment with methotrexate through 54 weeks with a median dose of 15 milligrams per week, which was no different than the baseline median values.

The efficacy results from the ATTRACT trial demonstrate that Remicade, in combination with methotrexate, unequivocally alters the course of rheumatoid arthritis and is clearly superior to placebo plus

methotrexate with respect to prevention of structural damage, the primary 54-week endpoint of the trial. And here are the results.

The median value for each treatment group is shown by the horizontal line in each box which represents the interquartile range. As you can see, the placebo group had continued progression of structural damage, with a median change in modified Sharp score of 4 from baseline to 54 weeks. By comparison, each of the four Remicade groups demonstrated little or no progression of structural damage, with median ranges in modified Sharp score of 0.5 to minus 0.5. These results were highly statistically significant with p values of less than .001, comparing each Remicade group to the placebo group.

Importantly, no clear evidence of a dose response was observed for the primary radiographic endpoint with 3 milligrams per kilogram every 8 weeks, demonstrating effects comparable to higher dose regimens. Thus the ATTRACT trial met the predefined 54-week endpoint, demonstrating that Remicade prevents structural damage.

The primary radiographic analysis you just saw represents changes following 1 year of treatment. However, as shown here, the ability of Remicade to prevent structural damage is observed as early as 30 weeks with the benefit fully sustained through 54 weeks. In contrast,

patients treated with placebo demonstrated progression of structural damage as early as 30 weeks with continued progression through 54 weeks.

Up until now, I've shown you the results as medians. Here are the results presented as means. The mean change from baseline in van der Heijde modified Sharp scores are shown for each treatment group on this slide. Again, a similar magnitude of effect is observed for each of the Remicade groups compared to placebo.

As I indicated, overall compliance with obtaining radiographs at baseline and 54 weeks was good, although some patients, particularly in the placebo group who dropped out early, did not return for their 54-week radiographs. Also, given the amount of preexisting joint damage and prior joint surgeries in this patient population, some radiographs, particularly of the feet, could not be assessed because all evaluable joints had prior surgery.

To assess the potential impact of these missing x-rays on the primary radiographic endpoint, additional analyses were performed. Several of these analyses are included in Centocor's or the FDA's briefing document. These included deriving results for missing data using extrapolations from available data and replacing missing values using worst-case assumptions. Results from these

analyses were robust and consistent in demonstrating that missing radiographs had no effect on the results of the primary radiographic endpoint.

As shown on the next three slides, the radiographic results were highly consistent across patient subgroups. Shown here are differences between the placebo group and the four Remicade groups combined in mean change in radiographic scores from baseline to 54 weeks depicted in this figure by the small vertical bars.

Because each of the four Remicade groups had similar effects with respect to prevention of structural damage, they are combined for these analyses. The 95 percent confidence intervals for these differences are depicted by horizontal bars. Vertical bars to the right of 0 indicate that Remicade was better, while bars to the left of 0 indicate that placebo was better. At the top of the chart are differences between placebo and Remicade for all patients. Regardless of gender, age, center location, or baseline dose of methotrexate, patients treated with Remicade responded better than patients treated with placebo.

Similarly, as shown on this slide, regardless of rheumatoid factor status, functional class, previous joint surgery or HAQ score at study entry, patients treated with Remicade did consistently better than patients treated

with placebo.

Of note, patients with early rheumatoid arthritis of 3 years or less showed radiographic benefits which were comparable to that of patients with rheumatoid arthritis of longer duration. Moreover, Remicade was effective regardless of the extent of structural damage at study entry. Thus, patients with baseline van der Heijde modified Sharp scores of less than 30, from 30 to less than 90, and 90 or above all obtained a similar degree of benefit.

Lastly, patients who were ACR20 responders, as well as nonresponders, had a similar degree of benefit. The results of these analyses underscore the consistency of benefit that Remicade, in combination with methotrexate, provides with respect to prevention of structural damage.

As demonstrated in the Wolfe and Sharp paper mentioned earlier, both components of the modified Sharp score, erosions and joint space narrowing, contribute to the long-term structural damage in rheumatoid arthritis. The next two slides show the effects of Remicade on each of these components.

Shown here, all Remicade dose regimens in combination with methotrexate prevented development of joint erosions through 54 weeks. In contrast, patients treated with placebo plus methotrexate continued to develop

erosions. No apparent dose effect is evident with respect to the Remicade groups. This analysis accounts for all worsening in erosions, including both new erosions in previously involved or uninvolved joints, as well as existing erosions that may have progressed.

Moreover, Remicade at all dose regimens in combination with methotrexate prevented further joint space narrowing through 54 weeks. As observed for erosions, patients treated with placebo plus methotrexate had continued progression of joint space narrowing. Each Remicade group was significantly better than placebo, but again, no dose effect between the Remicade groups was observed.

The ability of Remicade, in combination with methotrexate, to prevent both erosions and joint space narrowing is critically important with respect to being able to prevent further structural damage.

Additional prespecified endpoints in the ATTRACT trial were intended to assess the durability and magnitude of the clinical response through 54 weeks. As shown, all Remicade groups, including the 3 milligram per kilogram every 8 weeks group, demonstrate improvement in both the ACR20 and ACR50 responses compared to the placebo group, and this response is maintained through 54 weeks.

All Remicade regimens demonstrated similar

degrees of response early on and a continued similar degree of benefit at 30 weeks. Beyond 30 weeks, there was a trend towards a higher degree of response in the higher Remicade dose groups. However, all Remicade dose groups, not only at the 30 week but also at the 54-week endpoint, had statistically significant improvement in signs and symptoms compared with placebo.

The profound effects which I just presented with respect to prevention of structural damage are further supported by results from ATTRACT which demonstrate that Remicade, in combination with methotrexate, is superior to placebo plus methotrexate in improving physical function.

The ATTRACT trial utilized validated, accepted endpoints for assessing physical function, as recommended by the FDA guidance document, including the HAQ and SF-36. This figure shows the median improvement in HAQ disability index scores through 54 weeks by treatment group. All of the Remicade groups demonstrated improvement in HAQ disability index scores of 0.3 to 0.4 which was significantly better than observed with placebo. This degree of improvement in HAQ scores was greater than 0.25, which is generally considered to be clinically significant.

The beneficial effects of Remicade observed with HAQ are supported by the effects on quality of life, as measured by the SF-36, which showed statistically

significantly greater improvement in the physical component summary scores through 54 weeks, as shown in your briefing document.

The ATTRACT study was designed to assess the effects of Remicade over a 2-year period. The study recently completed the second year and results are now available. While these results have been shared with the FDA, they have not yet been formally submitted to the agency.

Treatment with placebo plus methotrexate led to continued and substantial radiographic progression through the entire 102-week period. In contrast, Remicade in combination with methotrexate at all four dose regimens was able to fully prevent radiographic progression not only through 30 weeks and 54 weeks, but also through 102 weeks.

This slides shows the mean changes from baseline in van der Heijde modified Sharp scores through 102 weeks. Particularly notable is the observation that patients treated with placebo had continued substantial and linear progression in structural damage. In contrast, patients treated with Remicade at all dose regimens had prevention of structural damage through 102 weeks.

Remicade, in combination with methotrexate, also sustained the reduction in signs and symptoms through 102 weeks, as well as sustained the improvement in physical

function.

Members of the committee, I would submit that these results are strong evidence in a randomized, double-blind, placebo-controlled trial of 2 years' duration for the ability of a drug to prevent structural damage and for the durability of these effects. Thus, Remicade demonstrably alters the course of rheumatoid arthritis and is superior to placebo in preventing structural damage. The primary radiographic endpoint of the trial was achieved.

Importantly, Remicade prevents both erosions and joint space narrowing. This effect is robust and consistent across dose regimens and patient subgroups, including those with early disease. The radiographic results that were observed are supported by a sustained reduction in signs and symptoms through 54 weeks.

Remicade, in combination with methotrexate, also improves physical function, as measured by the HAQ disability index and physical component summary scores of the SF-36 to a significantly greater extent than placebo.

The safety results from the ATTRACT trial demonstrate that Remicade administered over 1 year is safe and well tolerated. I would like to review the clinical trial experience, particularly with respect to adverse events and lab results from the ATTRACT trial, as well as

other clinical trials, with attention paid to infusion reactions, serious infections, and malignancies. I would also discuss adverse events that have been observed in post-marketing experience.

The clinical trials which demonstrated the safety of Remicade for the treatment of rheumatoid arthritis is provided by pooled safety data, which includes 771 Remicade-treated patients and 192 control patients. These data are derived from 12 completed clinical trials in 913 patients. Six of these trials were in rheumatoid arthritis and included 660 patients, 555 of whom received Remicade.

Safety data with respect to serious infections and malignancies also include long-term safety follow-up upon completion of treatment in these trials.

In addition, the post-marketing safety experience comes from more than 62,000 patients worldwide who have been treated with Remicade for Crohn's disease and rheumatoid arthritis through May of this year.

Shown here are adverse events which occurred in the ATTRACT trial in at least 10 percent of Remicade-treated patients. A further discussion of adverse events is provided in your briefing document. The incidence of one or more adverse events in patients was high among all treatment groups and not notably different when comparing

the Remicade groups to the placebo group. Upper respiratory infection, headache, sinusitis, coughing, rash, abdominal pain, fatigue, and pharyngitis were observed more often in the Remicade-treated patients. These events were generally mild to moderate in intensity and, as noted previously, did not lead to discontinuation of treatment at rates exceeding that of the placebo group.

Importantly, the adverse events observed through 54 weeks of treatment in the ATTRACT trial were the same both in type and incidence as those observed through 30 weeks of treatment which was the basis upon which Remicade was previously approved for signs and symptoms.

Infusion reactions were defined as any adverse event that occurred during or within 1 hour after the infusion was completed. Infusion reactions occurred in patients receiving placebo infusions, as well as those receiving Remicade infusions. Overall, the incidence was low in both groups, although higher in patients receiving Remicade. Thus, approximately 2 percent of placebo infusions were associated with an infusion reaction, compared with 4 to 5 percent of Remicade infusions.

Most of these reactions were mild to moderate and are similar to those observed during administration of intravenous immunoglobulins. Immediate hypersensitivity reactions were infrequent. Serious infusion reactions were

rare and patients tolerated infusions well with few patients discontinuing treatment because of an infusion reaction.

Shown here is the incidence of infusion reactions observed in ATTRACT by treatment cycle through 54 weeks. Of note, infusion reactions did not increase over time.

Serious adverse events were infrequent in the ATTRACT trial through 54 weeks, and the proportion of patients with 1 or more serious adverse event or serious infection did not differ between patients treated with placebo and those treated with Remicade. Of note, the smallest number of serious adverse events and serious infections was observed in the 3 milligram per kilogram every 8 week group. The most frequent serious infections, occurring in 2 or more patients, were bacterial infections, including pneumonia, cellulitis, urinary tract infections, bacterial infections not otherwise specified, and sepsis. While the numbers are small, a higher rate was observed in the Remicade group for cellulitis, bacterial infection not otherwise specified, and herpes zoster, while a higher rate was observed in the placebo group for serious urinary tract infections and sepsis. 2 Remicade-treated patients, one receiving 3 milligrams per kilogram every 4 weeks and one receiving 10 milligrams per kilogram every 8 weeks,

developed tuberculosis and coccidioidomycosis, respectively.

Shown on this slide is the incidence of serious infections, sepsis, and other infections of note in all studies with Remicade and through 6 months of follow-up upon completion of treatment. The number of patients with serious infections per 100 patient-years is shown. No increase was seen in the incidence of serious infections or sepsis in Remicade-treated patients shown in green compared to control patients shown in red for all studies. The incidence of other infections of note, which includes tuberculosis, fungal or opportunistic infections was low. In addition to the ATTRACT patient with tuberculosis, 1 additional patient in ongoing clinical trials was recently reported with tuberculosis.

Overall, there were few laboratory abnormalities observed through 54 weeks in the ATTRACT study. Patients treated with Remicade had mild increases in hemoglobin levels, which was a return toward more normal levels. Remicade-treated patients also had a mild to moderate decrease in neutrophils and a mild increase in lymphocytes and monocytes. However, these changes were within normal ranges. Significant drops in neutrophil counts were infrequent, transient, and not associated with development of infections.

In addition, mild decreases in alkaline phosphatase levels were observed.

Finally, minimal increases in AST and ALT were observed, with median values increasing from 2 to 4 units per liter.

A small proportion of patients treated with Remicade developed antibodies to double-stranded DNA. In ATTRACT through 54 weeks, approximately 10 percent of patients became positive for anti-double-stranded DNA. In other studies in rheumatoid arthritis and Crohn's disease, approximately 9 percent of patients became positive. However, development of clinical symptoms suggestive of drug-induced lupus is rare.

Only 3 of 771 patients, or 0.4 percent, in clinical trials have developed symptoms suggestive of drug-induced lupus. None of these patients had renal or CNS involvement and all symptoms resolved after discontinuation of study drug and appropriate treatment.

Auto-antibodies other than ANA and anti-double-stranded DNA have only been infrequently observed.

In previous Crohn's disease trials, 13 percent of patients developed antibodies to Remicade. In ATTRACT, approximately 8 percent of patients had antibodies to Remicade. The majority of these are low titer, and while there is a two- to three-fold increase in the risk of

having an infusion reaction in patients with antibodies to Remicade, these reactions are infrequently serious or lead to treatment discontinuation.

The first patients treated with Remicade were in 1992 and patients have been followed for up to 8 years. During this time, 1 patient developed a non-Hodgkin's lymphoma while on study in the ATTRACT trial prior to 30 weeks. 2 other patients, 1 rheumatoid arthritis patient and 1 Crohn's disease patient, developed non-Hodgkin's lymphoma during 3 years of long-term follow-up after completion of treatment, while 1 additional patient developed Hodgkin's lymphoma.

Investigators are encouraged to report cases beyond the 3-year long-term safety follow-up and one additional case of non-Hodgkin's lymphoma in a rheumatoid arthritis patient was reported 6 years after completing treatment with Remicade. This patient had received two doses of Remicade at 10 milligrams per kilogram 6 years earlier.

It must be recognized that the expected incidence of non-Hodgkin's lymphoma in rheumatoid arthritis is 2- to 20-fold greater than for the general population. Risk correlates with the overall severity of rheumatoid arthritis and use of immunosuppressants. This describes the patient population that has been studied in Remicade

clinical trials. Moreover, no relation between dose of Remicade and/or duration of treatment and the development of lymphoma has been observed. Thus, although continued vigilance needs to be exercised in assessing potential risk of anti-TNF therapies for inducing lymphomas, at present there is not evidence for an increased risk.

Shown on this slide are the expected and observed incidences of malignancies other than lymphomas, excluding basal cell and squamous cell skin cancers, in ATTRACT and all clinical studies with Remicade while on study and during long-term follow-up. The number of patients in the control and Remicade groups are shown, as well as the total patient years of follow-up. Based on the NIH SEER database of a general population, the expected number of malignancies other than lymphomas in patients in the ATTRACT study treated with placebo would be 1, while the expected number in the Remicade group would be 3. What was actually observed was no patients in the placebo group and 3 in the Remicade group.

Across all studies, 1 patient in the control group and 8 patients in the Remicade group would be expected to develop malignancies other than lymphomas. The observed number for the control group was 1, while the observed number in the Remicade group was 9. Thus, the observed number of malignancies in the Remicade group is

not different from the expected incidence.

The number of deaths per patient-years of follow-up, as well as the incidence of death per patient-years of follow-up, are shown on this slide for ATTRACT, as well as for all studies. As can be seen, the observed incidence of death in Remicade-treated patients compared to patients in the control group was lower, although not statistically different. The relatively high 1-year mortality rate in the ATTRACT trial placebo group underscores that this was a seriously ill patient population.

As previously mentioned, to date more than 62,000 patients with Crohn's disease and rheumatoid arthritis have been treated worldwide with Remicade. Thus, there is a substantial post-marketing safety experience outside of the completed and ongoing clinical trials. As shown on this slide, the reported number of patients with infections, serious infections, including sepsis, and other infections of note, such as tuberculosis or opportunistic infections, as well as malignancies and deaths, in post-marketing experience have been low, and the safety profile is consistent with the current package insert.

Besides the completed studies that I have discussed this morning, more than 6,000 additional patients will be enrolled in a number of ongoing or planned studies

in rheumatoid arthritis or JRA, as indicated on this slide. In addition, almost 8,000 patients will be enrolled in other studies in Crohn's disease, psoriasis, and other diseases. Thus, Centocor is continuing to develop a substantial safety database with over 14,000 additional patients to be included.

Recall that earlier in my presentation, I pointed out the lack of any marked dose response for ACR20 through week 30 or structural damage through week 54. However, a trend towards better ACR20 responses with higher doses was observed at week 54. An explanation for these results can be inferred from the following slides.

Shown here are Remicade serum levels for each of the four treatment regimens through 54 weeks. Following the induction regimen at 0, 2, and 6 weeks, stable trough serum concentrations are achieved from 14 through 54 weeks in all treatment groups. The lowest trough concentrations occurred with the 3 milligram per kilogram every 8 week group and the highest with the 10 milligram per kilogram every 4 week group. Both the 3 milligram per kilogram every 4 week and 10 milligram per kilogram every 8 week groups had intermediate and comparable trough serum concentrations. Of note, the stable trough concentrations through 54 weeks provides evidence that regardless of the dose regimen, antibodies to Remicade do not have any

appreciable impact on Remicade levels.

Analysis of the clinical response data and CRP concentrations at week 54, relative to the Remicade trough concentrations, reveal that therapeutic Remicade serum concentration is approximately .1 to 1 microgram per ml. As shown on the left, the highest ACR20 response rates occurred in patients with trough concentrations of at least 1 microgram per ml while, shown on the right, normal CRP concentrations were associated with Remicade concentrations of at least 0.1 microgram per ml.

This slide shows the interquartile ranges for Remicade serum concentrations through 54 weeks in the 3 milligram per kilogram every 8 week group. A proportion of patients after week 14 had trough serum concentrations below the estimated therapeutic range. In these patients, supplementation of the dose, either by increasing the dose or decreasing the infusion interval, may restore the therapeutic benefit if diminished.

Based on these observations, we propose the following dose recommendation. The starting dose should be 3 milligrams per kilogram given as an intravenous infusion, followed with additional 3 milligram per kilogram doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Maintenance of the clinical response in some patients might require decreasing the infusion interval or

increasing the dose up to 10 milligrams per kilogram.

In conclusion, in patients with active rheumatoid arthritis, despite treatment with therapeutic doses of methotrexate, Remicade at a dose of 3 milligrams per kilogram every 8 weeks, in combination with methotrexate, provides the following benefits through 54 weeks: prevention of structural damage, both erosions and joint space narrowing; sustained improvement in signs and symptoms; improvement in physical function and disability; and it is safe and well tolerated.

I would now like to have Professor van der Heijde provide her perspective on the radiographic results.

DR. VAN DER HEIJDE: Thank you, Dr. Harriman.

Mr. Chairman, committee members, and FDA, my main research interest has been the development of radiological methods to assess structural joint damage and application of these methods in clinical trials of therapeutic agents. I headed a team that designed and conducted the radiographic analysis in the ATTRACT trial.

This morning I will address the size and quality of the ATTRACT radiographic data set, discuss structural outcome measurements, and summarize some of the specific features of the ATTRACT data.

In my view, the size, completeness, and quality of the radiographic data sets in the ATTRACT trial was

sufficient to establish the radiological benefit of Remicade given in combination with methotrexate.

The primary radiographic data set comprised 349 patients, or 82 percent of the patients enrolled. The primary analysis of these data for the total van der Heijde modified Sharp score is shown on the left.

Additional patients were included in the analysis by extrapolating missing data in the feet from data available in the hands or vice versa. These data are shown in the middle panel.

Missing data at 54 weeks were extrapolated from data available at 30 weeks and these are shown in the right panel.

When including 398 of the 428 patients, or 93 percent of the total patients enrolled, the same results were observed as for the primary analysis. Thus, the ATTRACT radiologic data set was complete and also of sufficient size, given that highly statistically significant results were achieved in each of the Remicade treatment groups.

Consistent results were obtained between the two radiograph readers. In this slide, results from reader 1 are shown on the left and results from reader 2 are shown on the right. As you can see, the relative differences among the treatment groups were essentially the same for

both readers. This level of reader consistency, as well as the overall reproducibility of the data, further established the quality of the data.

The radiographic results from ATTRACT are robust. Differences among treatment groups were consistently reproducible when applying several sensitivity analyses to deal with missing data. In addition, excluding patients with medication changes from the analysis did not change the results. Overall, there was a high level of consistent benefit across patient subgroups as you just saw in Dr. Harriman's presentation.

I would like to comment on the importance of the contributions of bone erosions and joint space narrowing to assess structural damage. Bone erosions and joint space narrowing give independent and additive information regarding structural damage. As we have heard in Professor Maini's presentation, different pathologic processes may be involved in these components of damage. The van der Heijde modified Sharp total score captures both of these aspects. Therefore, it is more sensitive to change and more reliable than either of the individual components.

In closing, I would like to emphasize some of the specific features of the radiographic findings in the ATTRACT trial.

First of all, Remicade effectively prevents structural damage in a medically resistant population. In the recent meta-analysis, published by Drs. Anderson and Feltzen, the following three factors were associated with a decreased response to medical treatment in patients with rheumatoid arthritis. These were increased disease duration, more severe functional class, and a higher prior DMARD use. These are all characteristics of the ATTRACT study population.

When considering ATTRACT radiographic results in the context of recently reported results with other therapeutic agents, it is important to recognize the differences in the patient populations that were studied. This slide compares the patient population studied in the COBRA trial, a study evaluating the combination of methotrexate, sulfasalazine, and corticosteroids; the leflunomide US301 study, the etanercept ERA study, and the ATTRACT study.

Compared to the ATTRACT study, these other three trials studied patients with less disease duration, less exposure to prior DMARDs, enrolled only methotrexate-naive patients, and studied patients with less severe functional class and less severe radiographic damage. Thus, the ATTRACT trial has demonstrated a significant structural damage benefit in patients with established,

medically resistant disease.

In conclusion, the radiological benefit of Remicade has several specific features. It is effective in the medically resistant population and benefits both bone erosion and cartilage damage. The benefit is durable through at least 2 years and has been demonstrated under controlled, blinded conditions. In addition, Remicade provides a structural damage benefit in a broad spectrum of patient subgroups. Taken together, the data demonstrate that Remicade provides a significant structural damage benefit.

Thank you. I would now like to introduce Dr. St. Clair who will discuss the clinical perspective.

DR. ST. CLAIR: Thank you, Dr. van der Heijde.

Dr. Simon, members of the advisory panel, and FDA representatives. I appreciate the opportunity to provide a rheumatologist's perspective of infliximab therapy for rheumatoid arthritis. My clinical experience comes from participating as an investigator in two clinical trials of infliximab therapy for rheumatoid arthritis and more recently in the clinic with its commercial availability.

The arrival of infliximab to the clinic has filled a previously unmet need in rheumatology, namely the control of disease in patients who are not responding

adequately to methotrexate therapy. Methotrexate is often the DMARD of first choice for treating patients with aggressive rheumatoid arthritis. However, clinical experience has taught us that most patients treated with methotrexate do not achieve a satisfactory clinical response. Until recently, the options for treating such patients have been limited.

The results from the ATTRACT trial that you just heard show that the addition of infliximab to a stable dose of methotrexate affords rapid disease control and important clinical responses in 50 to 60 percent of patients with active disease. Moreover, it has been well tolerated and has excellent patient acceptability.

Although methotrexate is widely believed to be the most effective and best tolerated of the disease-modifying antirheumatic drugs, treatment with this medication does not stop the radiographic progression of disease. This fact is illustrated by the ATTRACT data, which shows that patients who are responding inadequately to methotrexate alone show radiographic progression of disease over 2 years.

This is shown on this slide. The mean change in Sharp score from baseline is plotted on the y axis and the 2 years' treatment observation period on the x axis. You can see that the patients taking methotrexate alone

showed continued radiographic progression of disease. By contrast, patients receiving the combination of infliximab and methotrexate showed very little x-ray progression of disease over this 2-year period. As a rheumatologist, I am struck by how flat this line really is.

These x-ray data nicely complement the clinical data and provide an important rationale for choosing infliximab in this clinical setting. The incremental benefit of infliximab in reducing the signs and symptoms of rheumatoid arthritis and attenuating the radiographic progression of disease supports the role of TNF-alpha in the pathogenesis of rheumatoid arthritis. Moreover, the extent to which infliximab and methotrexate decrease the radiographic progression of joint damage suggests this combination profoundly modifies the underlying disease process.

A patient does not express their improvement necessarily on the basis of the changes in their x-rays. Instead patients will tell their rheumatologist about how they are feeling, the extent of joint pain and swelling, what they are able to do and what they are not able to do.

In ATTRACT, improvement translated into reduction in pain, greater ease in performing activities of daily living, and increased vitality and social functioning according to the SF-36. The ATTRACT data shows a

significant improvement in physical function, as measured by the HAQ. So, we have mean HAQ scores here on the y axis, 2 years of treatment on the x axis, the placebo group, namely patients receiving methotrexate alone, and then the patients who were treated with infliximab and methotrexate. The improvement in the patients receiving infliximab, in addition to methotrexate, is evident at 6 months and is durable through 2 years of treatment. Patients appreciate this gain in functional capacity.

Although infliximab therapy for rheumatoid arthritis has obvious benefits, clinicians should be aware of the potential risks.

First, infusion reactions. In my experience, infusions have gone very well. Some patients may experience transient nausea or headache, but otherwise these infusions are very well tolerated.

Serious reactions are rare, although I will share with you one patient of mine who developed hives and difficulty swallowing. This reaction resolved after parenteral Benadryl administration, and the patient did well. But this one case does remind us that we need to be prepared to deal with serious allergic reactions, should they occur.

Second, autoimmunity. You have already heard that anti-double-stranded DNA antibodies develop in

approximately 10 percent of infliximab-treated patients, but lupus-like reactions are rare, they are reversible, and do not result in serious organ system disease. Overall, the development of autoimmunity during infliximab therapy does not appear at this moment to be a major concern.

Third is immunogenicity. Approximately 8 percent of infliximab-treated patients develop antibodies to infliximab. In reviewing the data, my conclusion is that the clinical significance of these antibodies is unclear. However, some caution may be warranted in retreating patients with infliximab because of the delayed hypersensitivity reactions that occurred with retreatment of patients with Crohn's disease. I would like to emphasize, though, that the gap between treatment courses in these patients was 2 years. About 25 percent of these patients developed delayed hypersensitivity reactions, but we didn't see any of these reactions in ATTRACT despite gaps in treatment of 3 to 4 months.

Fourth are infections. Concerns still linger about the possibility that infliximab therapy may predispose to infection. However, I'm reassured by the ATTRACT data showing that infliximab-treated patients did not have a higher incidence of serious bacterial infections than patients taking methotrexate alone. I am still concerned about the possible risk of opportunistic

infection, and I am aware of the cases of tuberculosis reported in clinical trials and in post-marketing surveillance. Rheumatologists need to carefully select patients for infliximab therapy and obtain additional diagnostic studies, as clinically indicated, to exclude infection. Infliximab infusions should be temporarily suspended for patients who develop clinically important infections. They may be restarted when the infections resolve.

Finally, malignancy. We've already heard that there was no increase in solid tumors. There have been three cases of non-Hodgkin's lymphoma in rheumatoid arthritis patients, but there's really no convincing data yet to link anti-TNF therapy with the development of lymphoma. We clearly need longer-term observations to clarify this question.

Now I'd like to make a few comments about the treatment approach.

For my patients, the initial dose will be 3 milligrams per kilogram, given at week 0, 2, 6, and 14. This is consistent with the philosophy of using the lowest effective dose, which may turn out to be safer than higher doses. We don't know yet for sure.

I think the data from ATTRACT can provide some guidance in dosing of individual patients during

maintenance therapy who do not achieve an optimal treatment response. For example, some patients may have a waning of their treatment response after the initial three doses because of declining serum trough levels of infliximab.

We know that the 3 milligram per kilogram every 8 week group had a lower proportion of ACR50 responders than the three higher dosage groups.

And we also know that analysis of the pharmacokinetic data suggests that a trough serum infliximab level of greater than 1 microgram per ml is associated with a higher likelihood of response. More than half the patients in this group had trough levels below 1 microgram, and about a quarter of these patients had undetectable trough levels at week 30.

We also need to know that 3 milligrams per kilogram every 4 weeks and 10 milligrams per kilogram every 8 weeks produced serum trough levels of greater than 1 microgram per ml in more than 80 percent of patients.

So, what are the options for boosting the serum trough levels of infliximab? Well, first you can increase the dose or you can decrease the interval. Clinicians should be aware that 3 milligrams per kilogram every 4 weeks uses less drug than 10 milligrams per kilogram every 8 weeks. Therefore, shortening the interval at some point may be more cost effective than increasing the dose all the

way to 10 milligrams per kilogram.

So, I'm not making an argument to obtain serum infliximab levels to monitor therapy but instead providing some rationale for allowing rheumatologists flexibility in dosing individual patients.

Rheumatologists welcome the addition of infliximab to their available therapeutic options for rheumatoid arthritis. The results from ATTRACT give us reason to believe that prevention of joint damage for patients with rheumatoid arthritis is a realistic therapeutic goal.

Thank you. Mr. Page?

MR. PAGE: Thank you, Dr. St. Clair.

To summarize our presentations, the ATTRACT trial met the predefined primary endpoint for prevention of structural damage and also demonstrated improvements in physical function. The benefits with respect to signs and symptoms were sustained to 54 weeks. This supports the following proposed indication: Remicade, in combination with methotrexate, is indicated for the reduction in signs and symptoms, prevention of structural damage, erosions and joint space narrowing, and improvement in physical function in patients who have had an inadequate response to methotrexate. The additions to the approved indication are shown in the bold face.

Mr. Chairman, this concludes our presentations. We appreciate your attention. We'll be glad to respond to any questions either now or later in the proceedings.

DR. SIMON: Thank you. I'd like to entertain just a few minutes of clarification questions only, no discussion, just clarification questions. Barbara? Please identify yourself.

DR. WHITE: Barbara White.

I'd like to ask this question of Dr. van der Heijde. X-rays were reviewed in sets. Is there some way by which the readers might become unblinded to the treatment given a set of x-rays?

DR. VAN DER HEIJDE: No. They were given a set of the same patients at the same time, but they were completely blinded to the order in which they received the set and also to treatment or patient identity at all. They were provided by Bioimaging who received x-rays, digitized the films, and just digitized images were sent to the readers.

DR. WHITE: The reason I ask is it would seem to me that if I were given a series of sets of x-rays and I know that all patients had active RA to start with and I knew that the drug worked for signs and symptoms of the disease, that if I saw a series of x-rays and I saw soft tissue swelling in each of the three sets of x-rays and I

saw another set of x-rays and had soft tissue swelling in one but not in two others, that I might become a bit unblinded.

DR. VAN DER HEIJDE: Well, but soft tissue swelling is not so easy to see on x-rays that you can really rely on that to unblind the treatment. I don't think that's a real issue.

DR. SIMON: Janet?

DR. ELASHOFF: Yes. I would like to have clarification with respect to the HAQ AUC scores because they're shown for every patient and no deletions for missing data. Also in the book it shows that the minimum is always 0, which would suggest that nobody ever got worse.

DR. DEWOODY: I'm Kim Dewoody from the Biostatistics Department at Centocor.

The HAQ analysis did several things. One, we took the change from baseline at each time point for each patient. When a patient had a visit where there was no data, they were assigned a score of 0 for that visit. If the patient discontinued follow-up in the study, was no longer coming in for visits, they were assigned a 0 score from that point forward for those visits. We then calculated the area under the curve. Oh, I'm sorry. Excuse me.

The other thing we did is because we were assigning 0's for patients that discontinued the follow-up --

DR. ELASHOFF: That's 0 change, not 0 --

DR. DEWOODY: Yes, 0 change from baseline. Yes, that's correct.

Because we were assigning 0 change from baseline for the patients that discontinued follow-up, we chose to truncate measurements for 0 for patients that are continuing follow-up so that we're not treating patients that are doing poorly and discontinuing follow-up different from patients who are doing poorly and remain in the study for follow-up. So, 0 change from baseline represents no change or worsening in the analysis.

We are also using a nonparametric method for analyzing this so that would appropriately deal with the fact that we're truncating the measurements in the analysis.

DR. KATONA: My name is Ildy Katona, and my question is for Dr. Harriman. I would like to ask for clarification on the chemistry measurements of liver enzymes, the minimal increase in the AST and ALT levels, what percentage or exactly what degree these minimal increases accounted for.

DR. HARRIMAN: As I indicated in my

presentation, the median increases in AST and ALT over the period of 54 weeks of the trial was 2 to 4 units per liter. We have a slide here which we can show which will demonstrate the changes in the AST and ALT levels over time. These increases, again I would underscore, were very small increases in the population of patients that were treated with Remicade.

DR. SIMON: Perhaps you can bring this back in a few minutes while you look for it. Would that be okay?

DR. HARRIMAN: Sure. We'll be happy to do that.

DR. SCHWEITZER: Mark Schweitzer. A question for Dr. van der Heijde.

Were both feet and both hands together, all three sets together, given to the reviewer at one sitting?

DR. VAN DER HEIJDE: Yes, that's correct.

DR. SIMON: I have two questions. One is your last slide of the entire presentation states your expected change in the label. I just wondered your take in that you're asking for improvement in physical function, and yet the guidance document requires 2 years of data. Why are you justified in asking for this with the data that you presently have?

MR. PAGE: I think there are two points I would like to make there. The guidance document does indicate

the importance of showing clinical improvements. Now, admittedly we already do have the signs and symptoms. In other words, showing x-ray prevention of structural damage by itself is not sufficient. So, at least we thought it was important to continue to emphasize the signs and symptoms and the functional damage.

We acknowledge exactly what you say in terms of the guideline. We were not sure, when the guideline was written, whether it was felt that one must have 102 weeks in order for it to be important or simply the fact that at that time, it was not certain whether one could even achieve such results earlier.

DR. SIMON: My second question is related to in that you've chosen to come to committee and to the FDA for a change in your label based on the ATTRACT data set, and that this particular data set is studying a group of patients who are nonresponders or failures of therapy in methotrexate, it would suggest to me that this specific patient population perhaps may be unique both biologically and clinically.

In that this particular patient population thus did response in this manner, it's difficult for me to understand the request that in fact perhaps, as you have suggested, that infliximab is perhaps better than methotrexate in certain responses. It seems to me that

we're not seeing any data that demonstrates whether methotrexate does or does not inhibit progression of disease in the population. We're just seeing it in a population that were nonresponders to methotrexate. These were individuals with very active disease despite methotrexate therapy.

Might you comment on that particular choice that you've made to come for this request with this particular data set and not waiting for some of the other data that you yet have in planning that would broaden out your observations?

DR. HARRIMAN: Mr. Chairman, if I could just comment. The indication that we are seeking in the current approved indication is for patients who have an inadequate response to methotrexate. So, that's the patient population for whom Remicade has been studied and for which the proposed indication would be appropriate. So, we do agree with the comments that you made.

I would also point out or just maybe perhaps remind the committee of Dr. St. Clair's point, which was that in this patient population, there is clearly an important unmet medical need here. So, we feel that it's important to provide this data to the committee and have the committee review it and make an assessment as to the appropriateness.

DR. WHITE: I have another question for Dr. van der Heijde. I need some help from you since I'm not used to these scores. What in your opinion is a reproducible difference in scores?

DR. VAN DER HEIJDE: Please, could you explain a little bit more?

DR. WHITE: Yes. For example, tables 21 and 22 that were provided to us show that one reader had a median difference over the 54 weeks of 5. That was the median difference.

DR. VAN DER HEIJDE: Yes.

DR. WHITE: And the other reader had a median difference of 3. I think that's what it was. So, that's a difference of 2.

So, if you had reader 1 read at 5.8 compared to reader 2 at 5 to 3, that's a 40 percent improvement. So, I take it that's not a meaningful difference. What kind of difference is meaningful if 40 percent isn't in reading?

DR. VAN DER HEIJDE: It's very well known that if you have different readers, they have different levels of what they are reading. That's what you see if you compare all readers that you have.

What's very important to look at is what one reader is showing as a result of the trial, because the difference was also seen in infliximab-treated patients.

So, if you have reader 1 and you compare the results from the infliximab-treated to the control, or you use reader 2 and you use infliximab-treated results to the control, you have similar results.

What we are usually looking at is the intra-class correlation coefficient for the absolute scores between two readers, and if that's higher than .8, then we think that's a reproducible result and that the readers have a good inter-observer variation. That was met by these two readers.

There are other ways to assess the differences between readers, and that's also to look at the smallest detectable. Then you also look at the measurement error between the two readers. Then you come to a higher absolute figure. But even if you apply this to this data set, which is a very high specific number, then still you have the same results.

DR. WHITE: If I could follow on that just a little beyond the context of this particular study because it's something we need to discuss later on. In terms of other studies in which we would be looking for changes, perhaps not a prevention but a retardation, from your experience what would be the requirements in terms of radiologic readings and differences?

DR. VAN DER HEIJDE: Well, there are two main

issues: if you are looking at the group level or at an individual patient level. So, if you are looking at a group level, then you are really looking at a statistically significant difference between the two groups. And I think that's the first thing you need to address, and if that has been addressed, then it's open for secondary analysis. Then you can look at patients on an individual basis.

For that, it has been proposed recently by OMERACT that you could look for the smallest detectable difference. You can calculate that on the measurement error based on the readers you use, and from that you can calculate the smallest detectable difference that can be observed apart from measurement error. By using that, you can define the proportion of patients that really progressed compared to those that did not.

DR. SIMON: Did you calculate the smallest detectable difference in this study?

DR. VAN DER HEIJDE: Yes, we did. It was 8.6. Applying this to the individual patients, that means that if you look to all infliximab groups, 6 percent of the patients had progression above that cutoff level. If you look to the methotrexate-treated patients, it was 30 percent of the patients who had an increase above that.

DR. SIMON: One last question.

DR. ELASHOFF: In terms of looking at the

adverse event rates, did you ever make a statistical test across the five groups of dose-response trend or did you only do the overall test and then proceed for additional tests? So, was there a dose response across the five groups ever statistically tested for those adverse event rates?

DR. DEWOODY: We did not test for a dose response. So, it's the comparison among the five treatment groups as an overall with the pair-wise.

DR. HARRIMAN: Mr. Chairman, we have that slide whenever you'd like to look at it on the liver.

DR. SIMON: Could we see it now?

DR. HARRIMAN: Yes. What's shown here in this slide is the change in AST during the 54 weeks. I apologize that the figure has very small bars and dots on it, so it's a little difficult to see. But just to describe -- and again, I apologize. The solid lines that are within the boxes are the median values. Let me just explain this to you. The five treatment groups are shown here as placebo and then 3 milligrams per kilogram every 8 weeks, 3 milligrams per kilogram every 4 weeks, 10 milligrams per kilogram every kilogram every 8 weeks, and 10 milligrams per kilogram every 4 weeks. This is the baseline values here, and then each of the time points, 2, 6, 14, 22, 30, 38, 46, and 54 weeks.

Now, again, the medians are shown as the solid lines, which you can barely see, and then the boxes are the interquartile ranges, and patients with outlier values are shown as individual dots. Although perhaps a little hard to see, the values over time were really not very substantially different, although again, as I mentioned, the medians changed minimally from 2 to 4 units per ml.

If I could see the next slide which is the ALT values and again difficult to see. And I apologize. The trends over time, as you can see, are pretty flat. There is really not any clear evidence of a trend upwards over time among any of the treatment groups.

DR. SIMON: Thank you.

We'd like to move on now with the FDA presentation.

DR. MATTHEWS: Well, now I would like to present the FDA review of the data submitted to the BLA for infliximab as a treatment for rheumatoid arthritis with attention to prevention of structural damage.

The review team consisted of Dr. George Mills who reviewed the radiographic data, our biostatistician who was Bo Zhen. The clinical pharmacology review was conducted by Lori Paserchia. The preclinical data were reviewed by Lauren Black. Our bioresearch monitoring was under the control of Debra Bower. Michael Noska was our

regulatory project manager, and I was the clinical reviewer.

For this presentation, I will review the indication and the dose that's in the label, provide a brief reiteration of the background of the clinical trial that you just heard, which I refer to as ATTRACT. Then Dr. George Mills will come up and review the radiographic data, and then I will return for a review of the clinical data.

The current indication for infliximab for the treatment of patients with rheumatoid arthritis states that Remicade, in combination with methotrexate, is indicated for the reduction in signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate.

The proposed indication is Remicade, in combination with methotrexate, is indicated for the reduction in signs and symptoms, the prevention of structural damage, including erosions and joint space narrowing, and improvement in physical function in patients with rheumatoid arthritis who have had an inadequate response to methotrexate.

The currently licensed dose regimen for the treatment of patients with rheumatoid arthritis with infliximab is to administer 3 milligrams per kilogram as an intravenous infusion, followed by additional infusions of 3

milligrams per kilogram at the second and sixth weeks after the first infusion, and then every 8 weeks thereafter. And Remicade should be given in combination with methotrexate.

As you heard, for the indication of rheumatoid arthritis, Centocor conducted a 2-year, placebo-controlled, randomized clinical trial where infliximab was given as adjunctive therapy to methotrexate. Patients were randomized to one of five treatment groups, either placebo and then three dose regimens of infliximab, 3 or 10 milligrams per kilogram given at every 4 or 8 weeks. The study drug was infused at 0, 2, and 6, and then every 4 weeks. Patients who were randomized to the infliximab every 8 weeks received placebo in the intervening 4 weeks. Again, this was all in conjunction with a background dosing of methotrexate of greater than or equal to 12.5 milligrams weekly.

There were three endpoints in ATTRACT. The first endpoint was improvement in signs and symptoms, and this was at the week 30 time point. These data were submitted to the agency and reviewed, and on the basis of our review, the product was licensed for this indication in November of 1999.

The purpose of this presentation, as you know, is for the prevention of structural damage, and the data that were reviewed in support of this claim were the week

54. Because the data were to be reviewed again at week 102, the statistical cutoff for the week 54 analysis is a p value of 0.025.

And then the improved physical disability or functional analysis will be reviewed by the agency when we receive the week 102 data.

428 patients were randomized to the ATTRACT trial. It was conducted at 34 sites in North America and Europe. As you heard, the predominance of patients were white women, and the median age was 54.

The patients were balanced for their ACR criteria across all treatment groups. The median number of swollen joints was 20 and the median number of tender joints for all patients was 31. The median duration of disease was 8.4 years. 37 percent of the patients had had joint surgery. 43 percent of the patients also had extra-articular manifestations of rheumatoid arthritis, with the most common extra-articular manifestation being rheumatoid nodules.

The 428 patients were evenly randomized across the five treatment groups.

This table presents patients who discontinued for each of the treatment groups, and by discontinuations, I mean that they stopped receiving infusions of study drug, although patients were to return at both week 30 and week

54 for the various evaluations at those time points.

The highest proportion of patients who discontinued therapy were in the placebo group, where 50 percent of the patients discontinued receiving infusions. The main reason, as you heard, was due to lack of efficacy.

Of the four infliximab treatment groups, the 3 milligram per kilogram every 8 week dosing group had the highest proportion of patients who discontinued. This was due to lack of efficacy.

I would just like to note that the least proportion of patients who discontinued of the four infliximab treatment groups was in the 10 q 8, and it was pretty much evenly distributed between adverse events and lack of efficacy.

Now, Dr. George Mills will take over the podium and present to you the radiographic data.

DR. MILLS: Thank you, Dr. Matthews.

We're going to look at the radiographic analysis for the BLA supplement submission. The radiographic protocol schema for this BLA submission were radiographs of the hands and wrists and feet at the time points of the baseline, 30 weeks, and 54 weeks.

The primary efficacy endpoint at 54 weeks, the variable analyzed, was the change from baseline to week 54 in the van der Heijde modification of the total Sharp score

according to two independent readers. These two independent reviewers developed two separate data sets, and there was no consensus interpretation between these two interpreters. All interpretations were fully blinded.

For situations in which x-rays were interpreted by only one of the readers, the score of that reader was utilized for the statistical analysis, and this did occur on occasion.

For the analysis of the primary endpoint, there was a comparison of all treatment groups to placebo at the .025 level, as well as an improvement over the placebo, that being methotrexate alone, group for at least one infliximab treatment group again at the .025 level.

Our population for the primary efficacy endpoint, as emphasized, the enrolled study population was 428 patients. Patients with paired evaluable x-rays were 349. In this case, they had x-rays of the hands and feet at baseline and at 54 weeks, and they had sufficient imaging quality to allow for reader evaluation.

This produced a nonevaluable patient population. As noted, there were 428 patients randomized. 349 patients were evaluated, and 79 patients were nonevaluable. 13 of these patients had complete sets of films, but no total Sharp score could be obtained by either reader. 66 of these patients had incomplete sets of

x-rays, for again a total of 79 nonevaluable patients.

To present the analysis of the primary efficacy endpoint for radiographic, I'll show you the total Sharp score for hands and feet, followed by the erosion score for hands and feet, and then the joint space narrowing for hands and feet.

This table is for the total Sharp score for hands and feet, again based on readers 1 and 2. Again, this is the change in the total Sharp score from the baseline to week 54. Our total population for patients evaluated in the methotrexate arm, 64 evaluated patients. For all infliximab regimens combined with methotrexate, there were 285 patients randomized across the four treatment groups.

The median value of this change for the placebo/methotrexate arm was 4.0, noting the interquartile range of 0.5 to 9.7 and the complete range of a minus or negative 4.5 to 61.0.

For the infliximab regimens combined with methotrexate, we have the 3 milligrams per kg q 8 weeks. This is 0.5. Again, the interquartile range, a negative 1.5 to 3.0, and the full range at a negative 9.8 to 37.0.

For the 3 milligrams per kg q 4 weeks, the median value is 0.09, and the interquartile range was a negative 2.5 to 3, and the full range was a negative 23.0

to 32.4.

For the 10 milligrams per kg q 8 weeks, the median value is 0.5 with the interquartile range at a negative 1.5 to 2.0, and the full range at a negative 11.5 to 12.0.

Finally, for the 10 milligrams per kg q 4 weeks, the median is a negative 0.5, and for the interquartile range, it's a negative 3.0 to 1.5, and the full range at a negative 13.4 to 8.5.

Also evaluated are all the infliximab regimens combined and for that, the median is 0.00, with the interquartile range at a negative 1.8 to 2.0, and the full range at a negative 23.5 to 37.0.

Based upon this data set for the total Sharp score for hands and feet, there is statistical significance demonstrated for all infliximab regimens combined with methotrexate as compared to the methotrexate/placebo.

Next for the erosion scores. First of all, patients evaluated for the methotrexate/placebo were 66 and for all infliximab regimens combined with methotrexate, 293 patients are randomized across the four treatment groups. I'll read you just the medians in terms of this evaluation.

The median for the methotrexate placebo group is 2.0. For the 3 milligrams per kg at q 8 weeks, it's 0.0. For the next, it's 0.00, 0.5, and a negative 0.5.

For the all infliximab regimens combined, it's 0.00.

Based upon these findings, there is statistical significance demonstrated for all infliximab regimens combined with methotrexate, as compared to the methotrexate/placebo arm.

Next for joint space narrowing of the hands and feet, in this 64 patients are evaluated for the methotrexate/placebo arm; 285 patients are evaluated across the four infliximab regimens combined with methotrexate. The median for the methotrexate/placebo is 1.5, and as you can see across all infliximab regimens combined with methotrexate, as well as the all infliximab regimens combined, the value is 0.00.

With this, joint space narrowing of the hands and feet, there is statistical significance demonstrated for all groups as compared to the methotrexate/placebo arm.

There are 79 patients that are missing from this evaluation, and we have performed sensitivity analyses for these missing patients. I'll review four of these sensitivity analyses with you. First, the worst case analysis, followed by worst outcome analysis, and then based upon the findings here, we performed a worst outcome analysis modified -- and I'll explain this change -- and then a percent radiographic progression analysis.

The worst case analysis, the most conservative

approach. For patients' data that were missing in the methotrexate/placebo arm, the assignment of the best progression score of any patient evaluated in the study was provided, and that's a negative 23.5. For the infliximab regimens combined with methotrexate, any patient value that is missing has been substituted with the worst progression score of any patient evaluated in the study, and that was 61.03.

Based upon these assumptions for the data set for this sensitivity analysis, the median score for the methotrexate/placebo arm is 1.25, and respectively, the median values are 1.0, 1.0, 0.56, and 0.00.

Based on the worst case analysis, no statistical significance is demonstrated for any infliximab regimen combined with methotrexate as compared to the methotrexate/placebo arm. Indeed, a very conservative analysis and with 79 missing patients and with 24 patients missing in the placebo arm, it was not anticipated that this data set would tolerate this.

We performed then a worst outcome analysis. Here all missing subjects in all patient groups are assigned the worst progression score of any patient evaluated in the study, and that was 61.03. Note the median score for the placebo methotrexate is much higher based upon the loss of 24 patients as dropouts in this.

Hence, we will see that this 8.63 median for the change in the placebo compares to 1.0, 1.0, 0.56, and 0.00.

Based upon this, the worst outcome analysis, there is statistical significance demonstrated for each of the infliximab regimens combined with methotrexate as compared to the methotrexate/placebo.

Our concern was that, indeed, because of these 24 dropouts in the placebo arm, we wanted to do another analysis, and that is the worst outcome analysis modified. In this case, for the missing infliximab patients, they are again given the worst outcome for progression of any patient evaluated at 61.03. For the missing placebo patients, however, they're given the original calculated median placebo value of 4.0.

Based upon this worst outcome analysis modified, the median value for the methotrexate/placebo arm is 4.0 again, followed by the median values for each group of 1.0, 1.0, 0.56, and 0.00.

With this, the worst outcome analysis now modified, statistical significance is demonstrated for all infliximab regimens combined with methotrexate as compared to the placebo/methotrexate arm.

The last sensitivity analysis that we performed was a percent radiographic progression analysis. Here the change in total Sharp score for any evaluated patient

greater than 0 is designated and established as evidence of progression. If the total Sharp score was missing for the 79 nonevaluable patients, these patients were assigned as no evidence of progression.

Based upon these modifications to the data set for the sensitivity analysis, 58 percent of the patients in the placebo/methotrexate arm are determined to have evidence of progression. Whereas, for the infliximab regimen plus methotrexate, across the 3 milligrams per kg at 8 weeks, 43 percent are assigned as evidence of progression. The 3 milligrams per kg at 4 weeks is 42 percent, the 10 milligrams q 8 weeks at 46 percent, and the 10 milligrams per kg at 4 weeks at 27 percent.

Statistical significance is demonstrated for the 3 milligrams per kg at 8 weeks, the 3 milligrams per kg at 4 weeks, and the 10 milligrams per kg at 4 weeks. No statistical significance from the methotrexate/placebo arm is demonstrated for the 10 milligrams per kg at 8 weeks.

A summary of other analyses that we have performed that I am not going to present for you today. For the hands only, we've evaluated the total Sharp score, the erosion scores, and the joint space narrowing. Statistical significance is demonstrated for all infliximab regimens combined with methotrexate as compared to the methotrexate/placebo arm.

For the feet only, the total Sharp score and the erosion scores were also evaluated, and indeed, all of these groups of infliximab regimens combined with methotrexate demonstrate statistical significance as compared to the methotrexate/placebo arm.

For the feet only, we demonstrated for the joint space narrowing no evidence of statistical significance as compared to the methotrexate/placebo arm. It is well to note that these patients did have advanced rheumatoid arthritis and that the evidence here may be clouded in terms of this evaluation by the onset of additional osteoarthritic changes.

Next I'd like to discuss prevention of radiologic progression.

This was prospectively defined in the protocol as an increase from the baseline in the van der Heijde modification of the Sharp score greater than the inter-observer measurement error of progression, the SDD, between the two readers as determined by using the limits of agreement methods of Bland and Altman of 1985. The SDD, as you heard earlier, was calculated from the two blinded interpretation data sets for this trial as approximately 8.6.

To present this data, we've put together this table. On the vertical is the percentage of patients

deemed to have evidence of radiographic progression from 0 percent to 100 percent. On the horizontal axis, cutoff points were assigned, beginning at 8.6, that being the SDD, to the 0 value, which was established when we did our sensitivity analysis for CBER, to a negative 8.6.

Based upon these various cutoff points, we then calculated the number of patients who would be assigned as radiographic progression, first for the all infliximab patient group, noting that at the 8.6, 6 percent of this patient population would be determined to have evidence of radiographic progression for all infliximab patients. This progresses up to 47 percent of these patients would be determined to have evidence of radiographic progression at the 0 percent cutoff, and finally at the negative 8.6, virtually 100 percent of these patients would have evidence of radiographic progression.

Comparing this now to the placebo arm, where 31 percent of these patients would be determined to have evidence of radiographic progression at 8.6, an approximate 30 percentage point difference, to 80 percent of these patients who would have evidence of radiographic progression at the 0 cutoff point, again approximately a 30 percent difference. As you can note, at each area along this, there's an approximately 30 percentage point difference between the all infliximab regimen as compared

to the methotrexate/placebo arm. To the right of this, you can see they obviously progress closer as we lose a number of patients in this evaluation.

The selection of any cutoff point in a singular fashion is very limited in this type of evaluation. We must be very careful to look at the entire population and look at the various cutoff points as we assess this. Selection of any individual statistical number is interesting, but again limited in this. Whether you titrate that in terms of the clinical evaluation or purely a statistical model, one has to be very careful to look across the spectrum of the population.

This concludes my presentation of the radiographic analysis. I'll ask Dr. Matthews to come back and continue. Thank you.

DR. MATTHEWS: The topics I'd like to cover in the review of the clinical data include the efficacy data generated in ATTRACT through week 54, with focus on the ACR response, the data in support of improvement of disability, and then also to discuss some of the clinical data in conjunction with the data for radiographic response, and then again to conclude with the safety data.

This table presents the ACR response both at week 30 and at week 54. As you can see, at week 30, a greater proportion of patients treated with infliximab and

methotrexate achieved an ACR response than those patients treated with placebo and methotrexate. These differences were statistically significant. As pointed out, at week 54, again a higher proportion of patients treated with infliximab compared to placebo achieved an ACR 20, and you can see a dose response.

Now, this table provides some idea of the durability of response using the ACR20 as an outcome measure for the different dosing regimens. If you focus on the 3 q 8 week dosing regimen, you can see that one-third of the patients had a response both at week 30 and at week 54. 9 percent of the patients gained a response between week 30 and week 54, but 17 percent of the patients, or 15 patients, lost their response between week 30 and week 54.

If you now look at the 10 milligrams per kilogram every 8 week dosing regimen, you see that 43 percent of the patients had a response both at week 30 and week 54. 16 percent of the patients gained a response, and in contrast to the 3 q 8, only 8 patients lost their response between week 30 and week 54.

Now, these differences in durability of responses between the 3 and the 10 milligram per kilogram every 8 week dosing regimens may be related to the pharmacokinetics. This slide presents the trough infliximab concentrations along the vertical axis in a

logarithmic scale for several of the time points along the horizontal scale in the weeks, again for the 3 and the 10 milligram every 8 week dosing group.

In these analyses, patients were categorized into three responses, either low, medium or, say, high. The open circles represent patients who never achieved an ACR20 response at that visit. Patients represented in the closed circles are those who achieved an ACR20 response or greater, but less than an ACR50 response. Patients represented by the closed boxes represent patients who achieved an ACR50 or greater response.

For both dosing regimens, patients who had detectable serum trough levels of infliximab achieved an ACR20 response or greater. If you look at the 3 milligram per kilogram every 8 weeks, you can see that patients who failed to achieve an ACR20 response tended to have low or even negligible detection of serum trough levels.

I'd now like to move on to the data for the disability. This is the measurement of Health Assessment Questionnaire data. I just would like to refresh everyone's memory regarding this. There are eight categories that consist of about two to four questions per category. The eight categories are dressing and grooming, arising, eating, walking, hygiene, reach, grip, and then just general activities. The patients are asked to score

anywhere from 0 to 3 for the different questions that compose these categories. A score of 0 implies that they have normal activity; 1, they feel that their activity is adequate; 2, they feel that that activity they're limited in; and 3, they just feel that they're unable to perform that task without some assistance. The final score is from 0 to 3 because it's added up and averaged.

The prospectively defined analysis for HAQ in the ATTRACT trial was an area under the curve analysis where the mean HAQ scores for each of the observation periods were added up and then divided by the total time of observation. As you heard, there was a statistically significant difference at week 54 for the area under the curve measurement between patients treated with infliximab compared to those treated with placebo.

We conducted an additional analysis, a landmark analysis, where we measured the change from baseline and week 54 for the HAQ score. Where patients had a missing data point at week 54, we carried forward their last observation. In these analyses, we did multiply the differences between baseline by negative 1, so that in these analyses, a positive value does imply improvement.

As shown on this table, the median change from baseline for patients treated with infliximab is higher than those treated with placebo.

Now I'd like to present some analyses of the clinical data in conjunction with the radiographic data. For these analyses, we defined radiographic progression as patients who had an increase from their baseline van der Heijde modification of the Sharp score or if they had a missing van der Heijde-Sharp score.

We looked at the radiographic data in conjunction with the two clinical response measurement outcomes, namely the ACR20 and the area under the curve analysis of the HAQ.

This two-by-two table compares the ACR response by ACR20, yes and no, to the x-ray progression. Just to reiterate, progression here is an increase from the baseline score for x-ray or if there were missing data.

If you focus just on the ACR20 responders, there were 176 patients who responded to an ACR20. Of these, 52 percent, or 91, had no x-ray progression by this analysis. However, 85, or 48 percent, of the patients did have some x-ray progression even though they did have a response by ACR20.

If you look at the first row for patients who had no x-ray progression, there were 150 patients who had such an outcome, and 91, or 61 percent, of these patients also had an ACR20 response. But it's medically noteworthy, though, that 39 percent, or 59, of these patients who did

not have x-ray progression failed to have an ACR20 response.

We next looked at a correlation between the ACR response and a change in x-ray score. If you look at patients who had an ACR20 response compared to those who did not, you can see that their mean change from baseline x-ray score was lower compared to those who did not have an ACR20 response by week 54.

We also did the same analysis for ACR50, and again you can see the patients who achieved an ACR50 response had a lower mean change from their baseline x-ray score.

We also looked to see if patients with most improvement in the HAQ score had a difference in their mean change of x-ray score from baseline compared to those patients who did not have as great a response for HAQ. In this analysis we calculated the area under the curve for each of the patients and looked at the top 10 percent, those patients who we expected would have the best area under the curve response for HAQ, and compared those to the remainder of the patient population. As you can see, the patients who did have a better response, the top 10 percent, did have a smaller mean change in their x-ray score from baseline.

I'd now like to move on to the safety database.

You've heard a lot of this, so I hope that this will just sort of summarize it for you. Our focus of attention for this presentation then is deaths, malignancies, infections, autoimmune phenomena, and infusion reactions.

There were eight deaths that occurred through week 54. Five deaths occurred prior to the week 30 time point, and then three occurred subsequent to that. As far as I'm aware, there are no further deaths after the week 54 time point.

Three of these deaths occurred in patients who were randomized to placebo. 5 patients had been randomized to infliximab. One death occurred in each of the treatment groups, but two deaths occurred in the 3 milligram per kilogram every 4 week dosing group.

The causes of deaths for patients who were treated with placebo include intestinal gangrene, arrhythmia, and cardiac failure. The deaths that occurred in patients treated with infliximab include pulmonary embolism. 2 patients died due to cardiopulmonary events. There was one case of tuberculosis, and one case of coccidioidomycoses, or valley fever.

Because of the concern regarding the infections, particularly what could be considered opportunistic infections such as tuberculosis and cocci, I'd like to just present a little elaboration on these

cases.

The patient who developed tuberculosis was a 63-year-old woman. She had been diagnosed 10 years prior with a history of rheumatoid arthritis. She was randomized to the 3 milligram per kilogram every 4 week dosing regimen and had received 8 infusions of infliximab.

5 months after her randomization, she developed fever and weight loss, and then 2 months subsequent to that, during the evaluation for lymphoma actually, she developed a cervical lymphadenopathy and presented again with a history of 2 weeks of night sweats. Biopsy of the cervical node confirmed the diagnosis of tuberculosis. She was subsequently started on anti-tuberculous medications and developed jaundice. Unfortunately, she suffered an aspiration event and required cardiopulmonary resuscitation, which was extremely complicated, and she died from anoxic brain damage.

The case of coccidioidomycoses occurred in a 70-year-old woman who had had a 19-year history of rheumatoid arthritis. She had been randomized to the 10 milligram per kilogram every 8 week dosing group, and she had received 11 infusions of infliximab up to week 38.

She was admitted around that time with a history of weakness, anemia, and confusion. For reasons that I'm not clear about, she was in preparation for a

gallbladder surgery. During that time, they found peritoneal granuloma in culture and I believe histopathology verified the diagnosis of cocci. I know the culture verified it. Unfortunately, she died 1 month later despite treatment with amphotericin.

There have been 5 patients diagnosed with malignancies. Three cases were reported to us by the week 30 time point, and all patients had received one of the 3 milligram per kilogram dosing regimens of infliximab. 3 patients had been treated with 10 q 4 weeks of infliximab, and the malignancies that occurred were a large cell lymphoma, a recurrent breast carcinoma, and 1 patient had both squamous cell and melanoma.

2 patients had been randomized to the 10 milligram per kilogram every 8 week dosing regimen, and the malignancies that occurred in these patients were a basal cell carcinoma and a rectal adenocarcinoma.

This table provides a breakdown of the occurrence of infections for the five treatment groups. As you can see and as you have heard, a higher proportion of patients treated with infliximab compared to placebo did have occurrence of infection. When you look at patients who were treated with an antibiotic, where it was felt that the physician at least believed that there was an underlying bacterial infection, again a greater proportion

of patients treated with infliximab had a rate of infections using that criteria. However, patients with serious infections -- there really was no difference between the placebo and the infliximab treatment groups.

Dr. Harriman has already presented these data to you regarding patients treated with infliximab who had serious infections and that occurred in 2 or more of the patients. As you can see, pneumonia was the most common, followed be cellulitis, pyelo, an unspecified bacterial infection, sepsis, and herpes zoster.

During the period of ATTRACT, through week 54, there has been one case of an autoimmune, and this occurred in a 48-year-old woman who had had an 18-year history of rheumatoid arthritis. She was randomized to the 3 milligram per kilogram every 8 week dosing regimen of infliximab. 2 weeks after her second infusion, she developed a rash, which did resolve by month 3. However, it recurred 1 month later, and at that time she did have a weakly positive ANA and a negative anti-double-stranded DNA.

There were no serious infusion reactions through week 54 of ATTRACT. This table does represent the infusion reactions for the different treatment groups. As you can see and as you have heard, the occurrence of infusion reactions was more common in patients who were

treated with infliximab compared to placebo. Most of these infusion reactions were nonspecific, although there were two cases of more severe infusion reactions.

Because of the concern regarding infections, we reviewed the post-marketing reports, focusing in on the infections. We reviewed these data that were reported to the agency through June 16th of this year. I believe there were 744 reports by that time. Of these, a total of 130 were due to infections, with 21 deaths. As you can see, the most common reports of serious infections were related to the upper respiratory tract, and by this, we defined it as bronchitis, sore throat, or sinusitis. There were lower respiratory tract infections, 10 cases of pneumonia.

I'd like to point out that we did have five cases of tuberculosis reported to us by that time point. I reviewed all of these. As you know, if any one of you have ever worked with post-marketing reports, they always tend to be more frustrating because you always want to ask more questions and you can't get any answers. But although some of the data is rather sparse, my review of it suggests that all these five cases were primary cases of pulmonary tuberculosis. There were no disseminated cases, but I have no data regarding exposure history or potential risks for tuberculosis.

There were 10 cases of fungal infections, and

these included aspergillus, histoplasma, pneumocystis, and candida. In candida, we also included oral candida.

There were 9 cases of patients reported who had had viral infections, and these included herpes simplex and I believe 2 cases of CMV.

In summary, review of the efficacy data indicates that treatment with infliximab delays the progression of structural damage through week 54, as measured for both erosion and joint space narrowing.

Review also indicates that treatment with infliximab provides a durable clinical response through week 54, as measured by the ACR20 outcome measure.

Review of the safety data suggests that the rate of infection is higher in patients treated with infliximab, although the rate of serious infections were comparable to those patients treated with placebo. There is a risk of infusion reactions. When you look at the adverse events that occurred between weeks 30 and 54, there was really no increase in the incidence of these safety events.

So, thank you.

DR. SIMON: Thank you.

I'd like to open up for questions of clarification to the FDA for a few minutes before our break. Identify yourself please.