FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

Open Session

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The Ballrooms
Holiday Inn Gaithersburg
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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (8:06 a.m.)

DR. ABRAMSON: I'm Dr. Abramson. I'd like to call the meeting to order and begin with a meeting statement by Kathleen Reedy, Executive Secretary.

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 exception. Dr. David Yocum is excluded from participating in today's discussion and vote concerning Enbrel. Further, in accordance with 18 United States Code 208(b)(3), a full waiver has been granted to Dr. David Felson.

A copy of this waiver statement 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 like to disclose for the record that Drs. Kenneth Brandt, Steven Abramson, and Lee Simon have interests which do not constitute financial interests within the meaning of 18 United States Code

208(a), but which could create an appearance of a conflict. The agency has determined notwithstanding these interests that the interests of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Brandt, Abramson, and Simon may participate fully in today's discussion and vote concerning Enbrel.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and 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. ABRAMSON: Thank you.

I'd like now to ask the committee members to introduce themselves.

DR. PUCINO: Frank Pucino with the Pharmacy Department at the National Institutes of Health.

DR. FELSON: David Felson, a rheumatologist-epidemiologist at Boston University Medical School.

DR. KATONA: Ildy Katona, pediatric

rheumatologist from the Department of Pediatrics, the Uniformed Services University of the Health Sciences.

DR. SIMON: Lee Simon, a rheumatologist at Harvard Medical School and Beth Israel Deaconess Medical Center in boston.

MS. MALONE: Leona Malone, consumer representative.

DR. BRANDT: Kenneth Brandt, rheumatologist, Indiana University School of Medicine.

DR. ABRAMSON: Steve Abramson, rheumatologist, NYU and the Hospital for Joint Diseases.

MS. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. HARRIS: Nigel Harris, Dean at Morehouse School of Medicine and a rheumatologist.

DR. ELASHOFF: Janet Elashoff, Biostatistics, Cedar-Sinai Medical Center and UCLA.

DR. MILLS: George Mills, Center for Biologics.

DR. JEFFREY SIEGEL: Jeff Siegel, Food and Drug Administration, Center for Biologics.

DR. SCHWIETERMAN: Bill Schwieterman, Center for Biologics.

DR. JAY SIEGEL: Jay Siegel, Biologics.

DR. ABRAMSON: Thank you very much.

We'd like to begin this morning's presentation

with that from the Immunex Corporation.

Dr. Viveash?

DR. VIVEASH: Good morning, members of the committee, FDA colleagues, and visitors.

We appreciate this opportunity to present to the committee comprehensive clinical and radiographic results from a trial of 632 patients with RA as the basis for modification of the current indications for Enbrel in RA.

Dr. van der Heijde will provide background information on structural damage in RA, how it is assessed in clinical trials, and how it's currently taken. Dr. Finck will present the design and results of the trial, and Dr. Garrison will present the safety profile of Enbrel since the initial approval in 1998 and the risk-benefit profile of Enbrel in RA.

We also have with us today four consultants. Drs. Alarcon and Paulus have extensive experience with trials in RA and treatment of patients with methotrexate.

Dr. Fisher is a consultant statistician who has substantial experience in active control trials and has served on the Cardio-Renal Advisory Committee.

Dr. Sharp served as x-ray image reader and consultant for the Enbrel early rheumatoid arthritis trial. The modified Sharp method was used to score the x-ray

images in the trial.

The development program for Enbrel has followed FDA guidelines. On the basis of three trials, Enbrel was approved by the FDA in November of 1998 for the reduction of signs and symptoms of moderately- to severely-active RA in patients who have an inadequate response to one or more disease-modifying anti-rheumatic drugs. Enbrel may be used alone or in combination with methotrexate.

In May of 1999, Enbrel was approved for the same indication in polyarticular course juvenile rheumatoid arthritis.

The FDA guidance for industry spells out the claims that a sponsor may request for the treatment of RA. These include the two claims that will be addressed today, reduction of signs and symptoms of RA and prevention of structural damage. The guidance also defines other claims, but these will not be addressed today.

The FDA guidance states that a trial designed for approval for prevention of structural damage must demonstrate slowing of x-ray progression using a validated radiographic index, such as the Larsen or modified Sharp method, or the trial should demonstrate prevention of new x-ray erosions by maintaining an erosion-free state or preventing new erosions.

You'll recall from the earlier slide that the

original label for Enbrel was based on studies in patients with RA who had failed DMARDs. Based on the results of the ERA trial, Immunex proposes that the label for Enbrel be amended to remove the requirement that patients need to fail other DMARDs before Enbrel can be prescribed. Therefore, Enbrel will become an option for initial DMARD therapy for patients with active RA.

Immunex proposes that the label for Enbrel be amended to "Enbrel is indicated for reduction in signs and symptoms and prevention of structural damage in patients with rheumatoid arthritis."

Now, I would like Dr. van der Heijde to share her clinical perspective on structural damage in RA.

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

I would like to discuss with you today aspects of RA that for most of you on the committee will seem very elementary. However, I hope that the background information I will present will give all of the committee members an understanding of how we assess structural damage in RA in clinical trials and how active RA is currently treated.

I'll briefly discuss the characteristics of joint damage in RA and the scoring method used in this clinical trial.

Next, I will discuss the consequences of

disease activity versus disease duration. Finally, I will touch on the ACR guidelines for the management of RA and the use of methotrexate.

Structural damage in RA has certain characteristics that are unique and are thought to be consequence of ongoing inflammation. These structural damages include periarticular osteopenia, erosions, usually at the bare areas between the insertion of the joint capsule and the area of the bone protected by thick articular cartilage, joint-space narrowing due to cartilage degradation and loss, joint subluxation and malalignment that are due to tendonlexity, intrinsic muscle wasting and joint damage, and, finally, total joint collapse and ankylosis may occur. All these abnormalities may occur in both small and large joints.

Slowing of radiographic progression of RA has become an established surrogate marker for overall patient benefit. Several methods for quantifying the rate of structural damage has been validated and used in clinical trials. The two most commonly-used methods are those of Larsen and Sharp and their modifications.

The Sharp method designs separate scores for erosion and joint-space narrowing, and these are added to derive the total Sharp score. This method has been found to be more sensitive to change over time and more

reproducible in patients with early RA compared to Larsen.

Originally, the Sharp method was applied to the hands and wrists only. Our group, as well as others, demonstrated that erosions were frequently present in the feet before they were present in the hands, and that more damage was seen in the feet compared to the hands.

Based on these observations, the Sharp method was modified in 1989 to include the feet as well as the hands and wrists.

The original Sharp method counted the number of erosions and the maximum erosion score for each joint was five, but counting erosions might not represent the degree of damage present. As illustrated here, one large erosion might represent considerable more damage than a few small erosions.

Over the years, the Sharp method for scoring erosions has been modified to incorporate the magnitude of the erosions as well as the number of erosions. Both of these modifications, the use of the feet and the magnitude of the erosions, are described in the literature and were included in the modified Sharp method used in the ERA trial.

Which patients are at risk to develop structural damage? Risk factors for rapid progression of structural damage in RA have been elucidated in several

trials, and these were most recently reviewed by Kim and Weisman in this year's March issue of Arthritis and Rheumatism.

These risk factors include the presence of rheumatoid factor and high disease activity which can be expressed as a high number of swollen joints or elevated acute phase reactants, such as CFP or ESR. Also, the presence of erosions early in the disease course indicates a higher risk of progression of structural damage. Specific haplotypes, such as the shared epitope, are additional risk factors, and, finally, extra-articular manifestations, such as nodules and vasculitis, although these are not frequently present in early disease.

Patients with one or more of these risk factors are likely to progress at a rapid, steady or linear rate.

The graph shown here is from the longitudinal observational study by Wolfe and Sharp from 1998. Patients with active early RA within two years of diagnosis were followed over 20 years. Here, we see the results of the first 10 years.

They received a variety of treatments during that time, and the Sharp erosion and joint-space narrowing scores show a linear progression pattern, and this continues for 20 years. Although some patients show more progression early and some later, the majority show a

linear progression.

Similar findings are reported in other long-term observational studies, such as those by Plant, Kareela, and Graudal. Progression of structural damage is mainly determined by disease activity, and it's not specific for certain time periods and course of the disease.

The ACR guidelines for management of RA states that active RA may lead to irreversible joint damage, even in the early months of the disease, and that disease-modifying antirheumatic drug therapy should not be delayed for more than three months in patients who, despite treatment with NSAIDs, continue to have joint pain, morning stiffness, active synovitis and persistent elevations of acute phase reactants.

The DMARDs included in the ACR guidelines are listed here. This list will probably be updated as newer agents that show prevention of structural damage are added to the list. An example is leflunomide, as it is the only DMARD currently labeled for retardation of structural damage.

Although methotrexate is not currently labeled for prevention of structural damage, it has become the first DMARD used by rheumatologists in the U.S. over the past decade.

Methotrexate has proven to retard structural damage in several studies. More details on these studies showing this are summarized in the briefing document.

The literature shows that the dose of methotrexate administered to patients in clinical trials has increased during the past 10 years. The higher dose of methotrexate used in clinical trials may reflect a change in the treatment paradigm for RA from one where DMARDs were avoided in early disease to one that aggressively uses DMARDs in early disease is recommended. This is in line with recognition that structural damage may occur very early in disease.

In summary, progression of structural damage in RA is a result of disease activity, regardless of disease duration. Patients with risk factors for progressive disease may demonstrate early rapidly-progressive joint damage.

Early aggressive therapies are recommended by the ACR guidelines for active RA, and rheumatologists in the U.S. are using methotrexate as a standard therapy.

Dr. Finck will now present the ERA trial design and results.

DR. FINCK: Thank you, Dr. van der Heijde.

I'm pleased to share with you the design and results of the Phase III trial of Enbrel versus

methotrexate in patients with active rheumatoid arthritis, the ERA trial.

The presentation will be as follows. After a brief description of the study design and the patient population, I will present the results for reduction in signs and symptoms and then for prevention of structural damage. This will be followed by safety.

To conserve time for discussion, I will not be covering the quality-of-life endpoints that were assessed in the ERA trial. These are in your briefing document, but if you're interested in these, I'll be happy to respond to your questions.

The ERA trial was a randomized multicenter double-blind trial comparing Enbrel to methotrexate in patients with rheumatoid arthritis. Joint assessors blinded to the treatment and other evaluations were used throughout the study.

An intent-to-treat design was utilized. Patients who came off of study drug received standard of care prescribed by their primary rheumatologist, but they remained in the study for evaluations.

All visits prior to and after discontinuation of study drug were used in the analysis, and patients were analyzed in the group to which they were initially randomized.

This slide shows the study schema. There were 632 patients who were randomized and received study drug, 207 in the Enbrel 25 milligram group, 208 in the Enbrel 10 milligram group, and 217 in the methotrexate group.

Now, the dose of oral methotrexate or an equivalent number of placebo tablets was rapidly escalated so that methotrexate would have its best possible performance in comparison to Enbrel. Patients started at a dose of 7.5 milligrams, and at four weeks, the dose was increased to 15 milligrams, and at eight weeks to 20 milligrams, if patients had any active joints.

Patients were allowed to decrease the dose of oral tablets once by five milligrams or two tablets for adverse events or sustained elevations of liver enzymes. All patients received folic acid, one milligram daily.

X-rays of the hands, wrists and feet were obtained at baseline, at six months, and at one year or if the patient discontinued study drug or evaluations, they were also obtained at that time.

The primary clinical endpoint was at six months, and the radiographic endpoint was at one year. The 10 milligram Enbrel group was included in this study at a less-effective dose. In all of the trials with Enbrel, a dose response to Enbrel has been noted with Enbrel 25 milligrams out-performing Enbrel 10 milligrams on all

clinical endpoints, and the presentation today will focus on the 25 milligram Enbrel group.

X-ray images were digitized, and they were presented to the readers on high-resolution monitors. Each case was read by two of six qualified physicians. There were five radiologists and one rheumatologist, Dr. Sharp. All of the readers were trained in the modified Sharp reading method, and the sequence of the films as well as the treatments for the patients was blinded to the readers.

The treatment groups were unblinded after one year when all patients had completed one year of evaluations. The open label trial is still ongoing, but the x-ray readers remain blinded to the treatment and to the sequence of the x-rays in the second year of the study.

To be eligible for this trial, patients could not have been previously treated with methotrexate, and at study entry, they had to be candidates for methotrexate, and that was defined in that they had to have active disease with no known contraindications for the use of methotrexate.

The 632 patients in this study all had rheumatoid arthritis of a relatively short duration, less than or equal to three years. Patients were also required to have active disease, and this was defined as at least 10 swollen and 12 tender joints.

Because we wanted to enrich the population in this study with patients who were likely to have erosive disease, they were required to be rheumatoid-factor positive at baseline, and if they were negative, they already had to have erosions present on their baseline x-rays.

With this degree of disease activity, inclusion of a placebo group into this study design did not seem reasonable or justifiable.

There were two co-primary endpoints in this study, reduction of signs and symptoms of rheumatoid arthritis and prevention of structural damage. In order to preserve the study alpha at the .05 level, both of these endpoints had to be achieved at the .05 level or if only one was achieved, it had to be at the .025 level.

The primary endpoint for prevention of structural damage was initially a superior endpoint that compared the change in Sharp erosion score over one year between all three treatment groups, and if the overall difference between all of the groups was significant, then the pairwise comparison between Enbrel 25 milligrams and methotrexate was to be evaluated. The study was designed, powered and conducted with the superiority endpoint.

Now, after discussion with the agency and four months before the study was unblinded, the primary endpoint

was amended to an equivalence endpoint requiring that Enbrel 25 milligrams not be inferior to methotrexate, based on a change in total Sharp score over one year.

Superiority with respect to erosions was moved to the secondary endpoint. The primary endpoint was changed because data became available during the trial that showed that methotrexate, when used as an initial DMARD, in patients with early rheumatoid arthritis prevented structural damage, and the magnitude of this response to methotrexate had not previously been reported.

After discussion with the agency, the following definition of non-inferiority or equivalence was agreed upon. Enbrel must preserve at least 70 percent of the expected methotrexate benefit.

The process of defining equivalence is represented schematically on this slide. Two assumptions were made based on the literature available at the time. One, that untreated patients with active rheumatoid arthritis, regardless of their disease duration, would progress at a steady rate of approximately six total Sharp units per year, and, two, that methotrexate-treated patients would progress at a rate of about two total Sharp units per year.

The difference between the expected rates of progression for untreated patients and methotrexate-treated

patients is the expected methotrexate benefit, and in this case, that's six minus two which equals four.

To demonstrate non-inferiority or equivalence in the ERA trial, Enbrel 25 milligrams had to preserve at least 70 percent of that expected methotrexate benefit or four. Enbrel could not be worse than methotrexate by 30 percent of the expected methotrexate benefit or 30 percent of four is 1.2 total Sharp units.

This value, 1.2, was set as the threshold for the upper limit of the 95 percent one-sided confidence interval for the difference between methotrexate and Enbrel that was going to be observed in the trial.

Now I will share with you the results of this trial. Patient characteristics as shown on this slide. The majority of patients were Caucasian women, approximately age 50, and approximately 15 percent of the patients were over the age of 65. Patients in this study had RA for a short time. In fact, the mean disease duration was less than one year.

To ensure that the groups were balanced, patients were stratified prior to randomization by their disease duration. Less than 18 months or 18 months to three years. Three-quarters of the patients were in the very early disease duration strata, less than 18 months. The groups were well balanced for all other baseline

characteristics as well.

Patients had very active disease at baseline. The mean swollen and tender joint counts were 24 and 30, respectively. The physician global and patient global assessments as well as the patient's assessment of pain were similar across the treatment groups, and they were approximately five to six units on a scale of zero to 10 for each of those assessments.

The baseline HAQ disability scores were approximately 1.5, indicating moderate disability, even in these patients with early disease. Acute phase reactants were elevated, and patients reported approximately four hours of morning stiffness.

The groups were balanced at baseline for patients with risk factors for progressive erosive disease. At least 87 percent of patients were rheumatoid-factor positive, and at least 85 percent already had erosions on their baseline x-rays.

The other predictors of progressive disease included acute phase reactants and swollen joint counts. These were elevated, and they were equally distributed between the treatment groups.

Compliance with all aspects of the study was excellent. This is shown on the following slides.

The investigators were compliant with dose-

escalating oral tablets, either methotrexate or placebo, as was required by the protocol. The methotrexate or placebo tablets were increased at four weeks and then again at eight weeks in each of the three treatment groups.

The median dose of methotrexate used in the ERA trial was 20 milligrams per week, and after dose-escalation, the mean dose of methotrexate was 19 milligrams per week.

The yellow line on this graph represents the methotrexate group, and the dose of methotrexate was decreased over the first year of the study for some patients on the protocol. 15 percent of patients on methotrexate had their dose of tablets reduced compared to only three percent of patients in the Enbrel group who had their dose of tablets reduced. This was per protocol.

Now, the reasons for dose reduction is shown in this slide. Adverse events and elevated liver function tests were the most common reasons for dose reductions. The treatment blind was maintained during dose reduction.

As stated earlier, patients could discontinue study drug, but they needed to remain in the study for evaluations. These patients did receive standard of care treatment, as I said, prescribed by their primary rheumatologist.

A very high proportion of patients, over 90

percent, completed one year of evaluations in the ERA trial, and over 79 percent of patients completed one year on study drug.

Discontinuation of study drug due to adverse events was significantly higher in the methotrexate group compared to the Enbrel treatment groups.

Compliance with x-ray acquisition was also excellent, except for one patient who had no x-rays and was not included in the x-ray analysis. There were no missing baseline films, and 98 percent of patients had at least two time points for evaluation, and 92 percent of patients had all three x-ray time points for comparison.

Next, I will discuss the results of the co-primary endpoints. The primary endpoint for reduction in signs and symptoms of rheumatoid arthritis was the area under the curve of the numeric ACR index.

We prospectively defined the area under the curve for the numeric ACR or ACRn as the primary clinical endpoint of the study, in order to follow FDA guidelines that suggested that methods that evaluated response over time were preferable to methods that just looked at the baseline and end of study observations.

The area under the curve for the ACRn allowed us to compare the cumulative response for the active treatment groups over the six months, the primary endpoint.

Now, the ACRn uses the ACR criteria with which rheumatologists have become familiar, and it is assigned a specific value for improvement, such as an ACR21 or an ACR48, in a matter that's analogous to that that's used to define an ACR20.

An example for the calculation of the ACRn is included in your briefing document, on page 34, and if you have questions about this, I can answer these during the question period.

But one can think of the area under the curve as the average percent improvement from baseline on the ACR criteria for each patient over the treatment interval. The continuous nature of the ACRn allowed us to calculate the area under the curve for each patient and then to compare the mean area under the curves between the two treatment groups.

This graph shows the mean ACRn at each time point for the Enbrel 25 milligram and for the methotrexate groups. The area under the curve for the ACRn for each group is represented in color. Blue plus yellow for the Enbrel 25 milligram group and yellow for the methotrexate group.

The difference in the area under the curve for the two groups over six months, the primary endpoint, was significant with a P value of .002, and it remained

significant over the entire year of treatment with a P value of .009. The primary endpoint for reduction in signs and symptoms of rheumatoid arthritis was achieved.

Now, the ACR20 has been used in clinical trials to define responders versus non-responders, and the percent of patients in the Enbrel 25 milligram group, the blue lines, and the methotrexate group, the yellow lines, that achieved ACR20, ACR50 and ACR70 responses is shown.

These results demonstrate that both Enbrel 25 milligrams and methotrexate are effective in reducing the signs and symptoms of rheumatoid arthritis in patients with active RA of a short duration.

A significant percent of patients treated with Enbrel 25 milligrams achieved these responses earlier in their treatment course and at a higher level, and they maintained these responses over the entire year of therapy. At all time points, the Enbrel group was numerically better than the methotrexate group on this landmark analysis.

But one can also calculate an area under the curve for the ACR20, 50 and 70, and when we do that, the Enbrel 25 milligram group is significantly better than the methotrexate group over the treatment interval.

The primary endpoint for prevention of structural damage was equivalence between Enbrel 25 milligrams and methotrexate with respect to the total Sharp

score over one year. This endpoint was also achieved.

This slide shows the equivalent endpoint results. The mean change in the total Sharp score over one year for methotrexate group was 1.3 total Sharp units, the yellow bar, and for the Enbrel 25 milligram group, it was 0.8, the blue bar.

The change in total Sharp score for both treatment groups is low, considering that the patients in the ERA trial had very active disease and risk factors for rapid progressive erosive damage. The difference between Enbrel 25 milligrams and methotrexate signified by the Delta sign is a negative 0.5, indicating that Enbrel 25 milligrams was numerically better than methotrexate.

The graph on the right of the slide represents the difference between Enbrel 25 milligrams and methotrexate, again the negative 0.5 units, and it shows the one-sided 95 percent confidence interval for that difference at 0.16. This is well below that threshold that we set at 1.2 that was necessary for Enbrel 25 milligrams to maintain 70 percent of the expected methotrexate benefit. In fact, Enbrel 25 milligrams maintained at least 96 percent of the expected methotrexate benefit.

As prospectively defined, the equivalence endpoint for prevention of structural damage was clearly achieved. Enbrel 25 milligrams slowed radiographic

progression in patients with rheumatoid arthritis at least as well as methotrexate.

Now, having demonstrated equivalence, the protocols specify that other endpoints would be evaluated. First, we evaluated the change in total Sharp score using the mean of the raw change scores adjusted for time on study. This analysis allowed us to evaluate progression over the first six months of the trial as well as over the entire year.

The rate of progression by total Sharp score was significantly less for the Enbrel 25 milligram group compared to the methotrexate group at six months, and there was a trend towards significance at 12 months.

The secondary endpoint superiority of Enbrel 25 milligrams to methotrexate with respect to change in erosion score over one year was also evaluated. To achieve this endpoint, a significant difference over all of the treatment groups and pairwise between Enbrel 25 milligrams and methotrexate was required. This endpoint was achieved.

Change in erosion score over one year for the Enbrel 25 milligram group and methotrexate group is represented on the bar graph here. Enbrel was superior to methotrexate with respect to preventing erosions. The overall P value for the three groups was .006, and for the pairwise comparison of Enbrel 25 milligrams to

methotrexate, the P value was .002.

For analysis of the change in erosion scores, we also used the mean of a change in the raw scores adjusted for time on study. Again, this allowed us to look at the change over six months as well as over the entire year, and as can be seen from this graph, Enbrel 25 milligrams was superior to methotrexate at six months, and this difference was maintained over the entire year, and the difference at both time points was highly significant, with a P value equal to .001 at six months and .002 at one year.

We also evaluated the percent of patients in each group who had no progression of erosions over one year. 75 percent of patients in the Enbrel 25 milligram group compared to 57 percent of patients in the methotrexate group had no increase in their erosion score over the full year. This difference was highly significant with a P value of less than .001.

In summary, the co-primary endpoint for efficacy, reduction in signs and symptoms of rheumatoid arthritis and prevention of structural damage, were both achieved. Enbrel 25 milligrams was significantly better than methotrexate on the area under the curve for the ACRn, indicating that Enbrel-treated patients had a faster onset of response, a higher magnitude of response and that this

was maintained over the entire treatment interval.

Enbrel 25 milligrams was shown to be at least equivalent to methotrexate with respect to change in the total Sharp score and superior to methotrexate in preventing erosions.

Finally, I will present the safety results for the ERA trial. I will include adverse events, serious adverse events, infections, malignancies and laboratory abnormalities.

Any problem or complaint that occurred while a patient was on study or within 30 days of discontinuation of study drug was recorded as an adverse event. The adverse events that were statistically associated with any of the treatment groups are shown on this slide.

Injection site reactions occurred in approximately one-third of patients who treated with Enbrel and in 7 percent of the controls. The injection site reactions were Grade 1 and Grade 2 in intensity. They occurred once in most patients and usually early in the treatment course, and they resulted in discontinuation of study drug in only one patient. This pattern and frequency of injection site reactions is similar to that that we've seen in all other controlled trials with Enbrel.

The adverse events that were associated with methotrexate are those that one would expect, nausea, rash,

and mouth ulcers.

In comparison, any complaint or event that required hospitalization, such as serious infections or malignancies, were recorded as serious adverse events. During the first year, 55 adverse events in 42 patients were classified as serious. 23 in the methotrexate group, 14 in the Enbrel 10 milligram group, and 18 in the Enbrel 25 milligram group.

However, the frequency and the rate of serious adverse events were similar in all three treatment groups. There were three patients who had deep venous thrombosis in the Enbrel treatment group, but all three of these patients had risk factors for DVT.

Of note, there were three patients in the methotrexate group who developed methotrexate lung toxicity during the first year of the study. This is described as interstitial pneumonitis on this slide. Methotrexate is an idiosyncratic pulmonary reaction that causes acute shortness of breath and infiltrates on a chest x-ray, and the rate of methotrexate lung toxicity in this study was 1.4 percent, and that's similar to what's reported in the literature for patients receiving methotrexate.

Infections were monitored closely throughout the study. The rate of all types of infections was higher in the methotrexate group, 1.9 events per patient year

versus 1.5. However, medically-important infections that required hospitalization or intravenous antibiotics occurred in less than 3 percent of patients in each group.

There were no opportunistic infections, and there were no deaths associated with infection in the ERA trial.

In over 600 patients, there was no apparent increase in the frequency of malignancies in any of the treatment groups. Patients were compared to an age- and sex-matched general population using the National Cancer Institute Surveillance, Epidemiology, and End Results Database, the SEER database.

We would have expected to see based on that database 1.8, 1.9 and two malignancies in the methotrexate, Enbrel 10 milligram, and Enbrel 25 milligram groups. There were two in the methotrexate group, two in the Enbrel 10 milligram group, and three in the Enbrel 25 milligram group.

The cancers that were reported were primarily those representing the most common cancer types that are seen in the general population, and they occurred at varying lengths of time of exposure to study drugs.

Now, as expected, the majority of laboratory tests were normal throughout this study, and the next two slides will show you the abnormal laboratory values that

are associated with any treatment group, and they include the worst value for an abnormal laboratory test for a patient at any time on study drug.

Remember that laboratory evaluations were obtained at each visit, up to nine times per patient, for the first year of the study.

Low lymphocyte counts were more frequent in the methotrexate group, and low absolute neutrophil counts were more common in the Enbrel 25 milligram group. However, for both low lymphocytes and low neutrophils, the percent of patients with a Grade 3 event was low.

Furthermore, the low lymphocyte counts and the low absolute neutrophil counts were sporadic, and they occurred in most cases at a single visit. Importantly, transient low neutrophil counts were not associated with serious infections.

Shown on this slide are the liver function test abnormalities, and as expected, they were significantly more frequent in the methotrexate group. However, Grade 1 and Grade 2 LFT abnormalities occurred in all treatment groups, and most patients in this study were on concomitant NSAID therapy, which may have caused some of these elevated tests.

Seven percent of patients on methotrexate and 1 percent of patients on Enbrel required a dose reduction of

their oral tablets as required under the protocol for an elevated liver function test. There were no Grade 4 laboratory abnormalities in any patient on study drug in the ERA trial.

As shown in previous studies with Enbrel, there were no treatment-emergent laboratory abnormalities in the Enbrel-treated patients that would suggest the need for routine laboratory monitoring.

The objectives of the ERA trial were to demonstrate the efficacy of Enbrel for the reduction of signs and symptoms of RA and prevention of structural damage. Both of these objectives were achieved.

Enbrel was also well tolerated in the patients with early active rheumatoid arthritis, and the safety profile of Enbrel compared favorably to methotrexate in this controlled trial. This was the first large head-to-head comparison of a biologic to methotrexate in patients with active disease and risk factors for rapidly-progressive erosive disease.

The data set is very complete with over 90 percent of the patients being evaluable for a full year of study, and the clinical and radiographic results are robust, and they demonstrate the efficacy of Enbrel in patients with active rheumatoid arthritis.

Dr. Garrison will discuss the risk-benefit of

Enbrel as an option for initial DMARD therapy for patients with rheumatoid arthritis.

DR. GARRISON: Thank you, Dr. Finck.

Rheumatoid arthritis is a chronic disease which is associated with significant long-term morbidity. Although there are good therapies available, a need still exists for new treatment options for patients and physicians.

The ERA trial was designed to address the question of whether Enbrel is another option for initial DMARD therapy. Specifically, is Enbrel an effective early intervention which will prevent structural damage as well as improve the signs and symptoms of rheumatoid arthritis?

In order to address these efficacy questions, which may expand the use of Enbrel, it is important to look at the entire risk-benefit profile of Enbrel.

The total number of patients treated with Enbrel is shown here. The Enbrel program has been conducted by Immunex in both the United States and Canada and by Wyeth-Ayerst in Europe, Australia and New Zealand.

I will review the global safety experience. At this point, over 1,800 patients have been treated in rheumatoid arthritis clinical trials for over 2,600 patient-years' exposure.

Over 700 patients have been treated with Enbrel

in studies of other diseases, and since FDA approval in 1998, it is estimated that over 65,000 patients have been treated with commercial Enbrel, with over 38,000 patient-years' exposure.

The length of Enbrel exposure is outlined here as well as the ICH guidelines. All rheumatoid arthritis patients in global clinical trials have been given the option to continue treatment with Enbrel. The length of Enbrel exposure decreases with time, not because patients have withdrawn from these studies but because they entered these trials at various time points, depending upon when their initial study ended.

At this time, over 1,400 patients have received Enbrel for 12 months or more, over 400 patients have received Enbrel for 24 months or more, and 53 patients have received three or more years of Enbrel treatment.

The majority of these patients, 82 percent, have been treated with Enbrel twice weekly 25 milligram injections continuously in an uninterrupted fashion for the entire length of time depicted here.

You have just seen safety from the ERA trial presented by Dr. Finck. In this large 632-patient study, Enbrel was safe and well tolerated, and, importantly, the safety profile from the ERA trial is consistent with all previous studies and with the current package insert.

Turning to safety in all RA studies, including the long-term open-label clinical trials and the United States' post-marketing experience, the same conclusions can be reached.

The safety profile of Enbrel from all these sources remains consistent with that from the controlled clinical trials and the current package insert, specifically regarding adverse events, serious adverse events, serious infections, and malignancies.

One theoretical concern about patients treated with anti-TNF therapies is that they may be more susceptible to infection, and as you know, in May of 1999, the Enbrel package insert was revised in coordination with FDA to ask physicians to be cautious when prescribing Enbrel to patients who have an increased infection risk.

As it is often difficult to interpret data from spontaneous adverse event-reporting systems, I'd like to now review all of our clinical trial data.

On this slide are the rates of serious infections from placebo-control trials from North America and from Europe in patients with longstanding DMARD-failing rheumatoid arthritis.

Serious infections are defined as infections requiring hospitalization or IV antibiotic therapy. The North American trials were of six-month duration, and the

European trial was three months long. From these controlled trials, the rate of serious infections is similar in the placebo and Enbrel groups.

Here added to the slide is the serious infection rate from the ERA trial, a 12-month trial. The rate of infections in the methotrexate group and the Enbrel group is similar. There is no evidence of a higher infection rate with Enbrel treatment from the controlled trials.

And, lastly, added to the far right of the slide is the serious infection rate seen in the post-marketing experience. It is important to remember that post-marketing events are spontaneously-reported, and unlike the clinical trial data, the true incidence is unknown.

However, the serious infection rate in the post-marketing experience is at a much lower level than that seen in the clinical trials, and the rate has been stable since Enbrel's approval.

Immunex has been working very closely with FDA to understand this information. As we have not seen any evidence of a higher infection rate in the RA patients enrolled in our controlled trials, a new clinical trial is ongoing, a 1,000-patient controlled trial which will enroll only patients with comorbidities, such as patients with

COPD or diabetes, to answer the question of whether there may be a subgroup that may require special caution or if these cases of serious infection are another manifestation of longstanding rheumatoid arthritis and its consequences.

Another question that has been raised is whether patients will have a higher infection rate with longer Enbrel treatment. Shown here are data from the North American trials on the top and the European long-term open-label treatment trials on the bottom.

Extended treatment of patients with very long-standing DMARD-failing rheumatoid arthritis, the rate of serious infections has remained stable over time and consistent with the rates from the controlled trials, and we are continuing to very carefully monitor these data.

Another theoretical concern about patients treated with anti-TNF therapies is that they may have a higher rate of malignancies. Generally, it takes five to 10 years to assess an increase in malignancy rates. In Enbrel clinical trials, there's no increase in malignancies.

Shown here is data from the North American studies, where we can apply the age- and sex-matched cancer rates for the general population from the SEER database. In over 1,200 patients, we would have expected to see 17.1 malignancies, and we have observed 17. In Europe, in over

600 patients, six cancers have been reported, also consistent with the cancer rates in the general population. These malignancies have been of various types, reflecting the most common cancer types in the general population, and of note, only one non-Hodgkin's lymphoma has been seen in the entire program. We are continuing to very carefully monitor these data.

In one of the questions to be discussed today, the post-approval safety studies are referred to. This large comprehensive program is outlined here, which will study more than 4,800 patients. Patients in the North American long-term treatment trials totalling 1,100 will continue to be evaluated for both safety and clinical efficacy for at least five years.

Patients originally in the ERA trial will also be evaluated for at least five years for safety, continued clinical efficacy and prevention of structural damage by yearly radiographs.

600 patients in Europe will continue to be followed in their long-term treatment trial, and the 1,000 patient comorbidity trial previously discussed is ongoing.

A 2,000-patient registry in Europe will begin this year, and in JRA, another registry of 600 patients will be started this year, in addition to studying in a controlled fashion the combination of methotrexate plus

Enbrel in the JRA population, and also a safety study in patients with systemic JRA.

We also have a large number of other programs looking at Enbrel in various diseases. Our largest is a program that's ongoing, evaluating Enbrel in chronic heart failure. The chronic heart failure trial, which will ultimately study 1,800 patients, has 800 patients enrolled at this point.

A DSMB meets regularly to monitor safety from this trial, and in all of these programs, over 2,000 patients are planned at this point to be studied. We will add other indications as these indications become more formalized. This information will add valuable data to our understanding of Enbrel and Enbrel's risk-benefit profile.

As for benefit, responses to Enbrel have occurred quite rapidly within the first weeks to months. Shown here on the dotted blue line are the swollen joint counts for the 25 milligram group from the ERA trial.

The rapid reduction in swollen joints is similar to the response seen in the long-term treatment trial in patients with many years of rheumatoid arthritis, and our expectation is that this benefit will be maintained for the ERA patients as it has been in patients with longstanding disease.

Not only is the treatment benefit rapid, but it

is also very consistent. Shown here are the ACR20 results for all clinical trials. On the left-hand column shows the percent of patients achieving an ACR20 response from the Enbrel 25 milligram group from the ERA trial, and to the right are the results from other controlled trials in DMARD-failing adults treated with Enbrel alone or with Enbrel plus methotrexate, and in JRA. Large numbers of patients achieved ACR20 responses quite consistently.

Similar consistency is seen in the ACR50 responses with Enbrel treatment. In all patients, regardless of duration of disease, extent of prior therapy or age, the results are remarkably consistent and show substantial benefit.

The continued benefits of Enbrel treatment are also outlined here, where the percent of patients achieving complete improvement, zero tender joints, zero swollen joints, and a zero or normal HAQ are displayed.

The ERA trial results at six and 12 months are on the left, and the responses in patients with longstanding DMARD-failing RA for up to two and a half years are on the right.

In both the ERA trial and in patients with longstanding disease, Enbrel's benefit is clearly maintained with longer treatment, and of note, patients receiving early intervention have more marked improvement

in disability, underscoring the benefits of early aggressive treatment.

From the ERA trial, Dr. Finck has shown us that in this large very complete data set, that Enbrel was superior to methotrexate at six months by total Sharp score and at six months and one year by erosion score.

As mentioned by Dr. Finck, the second year of this trial is ongoing. The data available to date from approximately two-thirds of patients continues to show maintenance of Enbrel's effect on markedly slowing the progression of disease as measured by the total Sharp score.

The last patients have just had their two-year films taken last month, and we expect that the full data set will be analyzed in the next one to two months. Just as the clinical benefits of Enbrel are sustained, so are benefits on prevention of structural damage.

Here are results at two years on the erosion scores for the methotrexate and 25 milligram Enbrel groups. The Enbrel group has very little change in the erosion score over two years. Enbrel's effect on prevention of structural damage is sustained with continued treatment.

Seventy-five percent of Enbrel-treated patients had no progression in erosion score over the entire one year of the trial, compared to 57 percent of patients

treated on methotrexate. These were patients with quite active aggressive disease, predicted to progress at a very rapid rate. Enbrel is clearly effective in preventing the structural damage associated with this chronic, debilitating disease.

In our initial presentation to this committee about a year and a half ago, we demonstrated that Enbrel had a very acceptable safety profile compared with placebo in patients with longstanding disease. These same conclusions can now be extended to patients with shorter disease duration as compared to methotrexate.

In addition, Enbrel is safe in the elderly, in children, and with chronic use.

Enbrel therapy provides significant clinical benefits, a very rapid effect, substantial, consistent and sustained responses, and now the ERA trial has demonstrated that Enbrel treatment prevents structural damage.

Based on these comprehensive data shown today, we propose that the restriction that patients must fail other DMARDs before Enbrel is prescribed be removed, and that Enbrel be an option for physicians to choose as treatment for their patients who need initial DMARD therapy.

We suggest that the label for Enbrel be revised as follows: "Enbrel is indicated for the reduction in

signs and symptoms and the prevention of structural damage in patients with rheumatoid arthritis."

And we would now like to address any questions that you may have.

DR. ABRAMSON: Thank you, Dr. Garrison.

I think what we'll do is hold questions for now and ask Dr. Siegel, Jeff Siegel of the FDA, to make a presentation.

DR. JEFFREY SIEGEL: Good morning.

My name's Jeffrey Siegel. I served as the clinical reviewer for this biologic license application. The other people who were members of the review team are shown on this slide.

George Mills reviewed the x-rays. Boguang Zhen was the biostatistician involved. Susan Giuliani was the project manager. Debra Bower was responsible for bioresearch monitoring. David Green was the pharm-tox reviewer. Lisa Rider served as consultant.

Currently in the package insert, the indication stated for Enbrel is as follows: "Enbrel is indicated for reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs. Enbrel can be used in combination with methotrexate in patients who do not respond adequately

to methotrexate alone."

The current BLA seeks to extend the label in two ways. First, it seeks to extend the indication to signs and symptoms in patients with early rheumatoid arthritis. Second, it seeks a general claim of prevention of structural damage.

In my presentation today, I'll cover five areas. First, I'll briefly cover the trial design. Then I'll talk about certain modifications to the protocol which you've already heard somewhat about. Then I'll talk about some background information on the radiographic endpoints. Then I'll discuss the efficacy and then, finally, the safety results.

In its presentation, Immunex has already described to you in some detail the design. I won't go over the design in detail. Suffice it to say that this was a trial carried out in patients with early highly-active rheumatoid arthritis, patients at risk for x-ray progression.

It was originally designed as a superiority trial, and it involved a head-to-head comparison with an aggressive dose escalation regimen of methotrexate.

There were two co-primary endpoints for this trial. The first was the clinical signs and symptoms endpoint, based on the ACRn area under the curve for the

first six months, which has already been described to you.

The second co-primary endpoint is the radiographic endpoint, and as originally stated, this was based on an improvement in erosion scores at 12 months.

Because there were two co-primary endpoints, the statistical plan called for using the Hochberg method of assessing statistical significance. Using this method, both endpoints must achieve statistical significance at the .05 level or, if either one does not, the other one must achieve statistical significance at the .025 level to be considered significant.

There were three additional endpoints, disability based on the Health Assessment Questionnaire or HAQ, health-related quality of life based on the SF36 questionnaire, and major clinical response.

Now I'll talk about the modifications to the protocol which took place while the trial was ongoing but before the trial was unblinded.

During the trial, the agency discussed with Immunex evidence from recent reports that many patients with early rheumatoid arthritis who were treated with methotrexate developed few, if any, erosions. This, of course, raised the possibility that Enbrel may not show superiority in the trial simply because the active control arm had little x-ray progression.

The agency asked Immunex if it would wish to seek an approval based on non-inferiority in the event that the study did not demonstrate superiority to methotrexate.

Furthermore, the agency noted that the basis for a non-inferiority determination should be stated prospectively.

Immunex revised its analytic plan of the radiographic endpoint to a demonstration of non-inferiority. At the same time, they changed the variable for the x-ray primary endpoint from erosion score to total Sharp score -- total Sharp score, of course, being a composite of the erosion score and a measure of joint-space narrowing.

The reason for the change in the primary variable was the data were unavailable to establish an effect size for erosion score, but there were data to determine an effect size for methotrexate for the total Sharp score.

I need to talk a little bit about non-inferiority trials and how they differ from the usual trials that we deal with, namely superiority trials.

In some clinical settings, efficacy may be demonstrated for a finding of non-inferiority in an active controlled trial but only certain very specific circumstances.

It's important that reproducible historical experience indicate that in a trial with a given design, that the active control arm will reliably give a result of a given size.

The principles used to evaluate a non-inferiority trial are shown on this slide. First, based on several historical controlled studies, the effect of the active control is established, and that's shown here with the point estimate and the confidence interval.

Then a margin of the tolerated level of non-inferiority is stated, so that the study can be analyzed statistically. This is set as generally at least 50 percent to be sure that the effect of the new therapy is at least better than non-treatment, and it may be set at levels greater than 50 percent in many cases, as was done in this trial.

But the point is that the margin is the level of non-inferiority which is to be excluded in the analysis. In this case, non-inferiority level of 70 percent was set.

Now, to show you how the results are analyzed, look at the various points and confidence intervals shown below. If the study agent has a greater effect than the active control, then the difference between the new drug and the active control will be negative, as shown here, and if the confidence intervals exclude zero, it can be

concluded that the new drug is superior to the active control.

If the difference between the new treatment, the study agent, and the active control is less, then the point estimate will be closer to zero. If, in this case, the confidence interval, the upper limit of the confidence interval, excludes the margin of non-inferiority, then it can be concluded that the new drug meets the non-inferiority standard.

In contrast, if the effect with the new drug is less than that with the active control, then the difference will be positive, and the confidence intervals may not exclude the stated tolerated margin of non-inferiority.

This slide shows a summary of this, about exactly what steps need to be taken to establish non-inferiority. First, it's necessary to determine from historical trials that the active control reliably has an effect of at least a certain size.

Next, the planned trial design should be similar to that of prior trials, including the stage of disease, concomitant therapy endpoint and other important variables.

Then a non-inferiority margin is set, which is the margin to be excluded, smaller than the total active control effect, and, finally, it's critical to ensure

appropriate trial conduct. This is particularly important because if the effect size for the active control in the new study is lower than it had been in the historical controlled trials, one may conclude that there is equivalence between the two, but that may not actually reflect a therapeutic benefit of the new agent.

Immunex derived an effect size for the active control arm, namely the methotrexate arm, from several studies. These included a multiyear observational study of recent onset rheumatoid arthritis published by Wolfe and Sharp in 1998, and a three-arm randomized controlled study which compared placebo, methotrexate and leflunomide.

I need to point out that the first study had neither an untreated arm nor a methotrexate arm. So it cannot reliably estimate the effect size for the current trial.

I also must point out that the second study used a different patient population than the current study and used a significantly-different methotrexate dosing regimen.

The assumptions for the non-inferiority analysis in this trial were as follows. It was assumed that the mean yearly progression rate was approximately six units per year based on the total Sharp score in untreated patients.

It assumed the mean progression rate on methotrexate of approximately two units per year, and the margin of non-inferiority to be excluded was 70 percent, namely the Enbrel arm should preserve 70 percent of the methotrexate benefit, meaning ruling out a difference of 1.2 units per year, and Immunex in their presentation went over the calculation of 1.2.

I need to point out that there are some limits to the non-inferiority trial design. First, historical controls in this case do not provide reproducible data to establish an effect size for the methotrexate arm.

The effect size for methotrexate is based on different patient populations from the current study. For example, the patients in this study had a shorter duration of disease and, as I mentioned before, a different methotrexate arm was used.

So in conclusion, because it's impossible to formally establish a minimal effect size, non-inferiority cannot per se be taken as evidence of efficacy. Therefore, interpretation of the trial must be based on the totality of the data, including additional analyses.

In this slide is shown the FDA analysis of the disposition of subjects. You can see there are approximately just greater than 200 patients randomized, between 207 and 217 of these patients received at least one

dose, and this constitutes the modified intent-to-treat population. No bias was introduced in the people who were randomized but not treated, and, finally, greater than 90 percent of all subjects completed a full 12 months of evaluations.

I will not be describing the baseline demographics since these were covered in detail by Immunex, but we have no major differences with the data presented by Immunex.

I will just mention that we saw no important imbalances in the level of disease activity or in the baseline demographics.

I'll also point out that the prespecified stratification variable of duration of disease had patients distributed with three-quarters in the shorter duration of disease, up to one and a half years, and a quarter of the subjects were in the longer duration of disease, one and a half years to three years, and there were no imbalances, and the patients, as mentioned, had highly-active disease with many active joints.

The radiographic procedures are described on this slide. Hand and foot films, as you've heard, were obtained at baseline, at six and 12 months. The radiographics were read by six trained readers in blinded random order. The correlation coefficient between readers

was high, as measured at 0.8.

The agency review of the radiographs showed that the data were complete and of uniformly good quality, and the readings were generally consistent and accurate.

We will not be discussing the reading of the radiographs in any more detail, but if you have any questions, George Mills is here to help answer them.

Now, the primary endpoint analysis specified a mixed model, which estimates a mean annual x-ray progression rate using the zero-, six- and 12-month films as well as baseline covariates.

As I mentioned before, the non-inferiority analysis was designed to exclude a margin of inferiority of 1.2 units per year or greater in the total Sharp score, and the protocol specified a sequential test of first non-inferiority, and then, if that had been demonstrated, then superiority.

The point estimates and 95 percent two-sided confidence intervals are shown on this slide. The methotrexate arm had a rate of radiographic progression of 1.33 units per year based on the total Sharp score. The Enbrel 25 milligram arm, the increase in the total Sharp score was less at 0.8.

The difference in the mean progression rate is to determine whether non-inferiority had been demonstrated

or shown on this slide. Above is shown the two-sided 90 percent confidence intervals of the difference between 25 milligrams and methotrexate.

As mentioned before, the difference is minus 0.5, and the upper limit of the 90 percent confidence interval is 0.16.

Using the more stringent two-sided 95 percent confidence interval, shown below, the upper limit of the confidence interval excludes a margin of inferiority of 0.29.

Thus, the test of non-inferiority in this study excluded a margin of greater than 1.2 units per year, with a maximum outer bound of actually less than that, of 0.29. A test of superiority of Enbrel 25 milligrams to methotrexate, however, does not reach the statistical significance using this analysis with a P value of .21.

Because of the limitations I mentioned before of a non-inferiority analysis in this setting, we must look at additional data to assess efficacy, especially secondary endpoints assessing superiority of Enbrel to the active control arm.

I'll be presenting to you the prespecified stratification by disease duration, using the prespecified radiographic endpoint, and I'll also be discussing the components of the total Sharp score and the erosion scores

and joint-space narrowing. Then I'll discuss differences in the rate of progression in the first six months of the trial compared to the second six months, and, finally, I'll discuss with you the subjects who had no radiographic progression.

Shown here is the rate of radiographic progression using the total Sharp score and the originally prespecified mean mixed model for the two prespecified stratification groups, patients with disease duration of less than 18 months and 18 to 36 months.

There was little difference between Enbrel 25 and methotrexate in the group with disease duration of less than 18 months. In the group with disease duration greater than 18 months, the rate of radiographic progression was less in the Enbrel arm, Enbrel 25 arm than the methotrexate arm, and the nominal P value for the pairwise comparison here is .03.

As I mentioned before, the total Sharp score is a combination of erosion scores and joint-space narrowing. When the erosion scores are considered separately in Enbrel versus methotrexate, the point estimate for Enbrel was .4 compared to 0.9 for methotrexate, and the P value was .047. Again, this is using the mixed model for an estimate of the difference between the means.

However, no difference at all was seen in the

degree of joint-space narrowing. This estimate was 0.4 units per year for both groups, and I should mention to you that the comparison of the erosion scores was the originally-specified primary endpoint for the trial before the analysis was modified.

Next, the agency wanted to look at whether the rate of x-ray progression differed at the beginning of the trial compared to the second half of the trial. When we examined the data, we saw that there were substantial skewing of the data which actually violated the assumptions of the mixed model.

What I'm talking about here is that if you look at the rate of x-ray progression, most of the patients had very little x-ray progression, approximately zero. However, there was a small subset who had substantially greater degrees of x-ray progression, hence the skewing.

Therefore, the agency believed that a nonparametric test for differences was more appropriate than using a test of means which requires an assumption of normality.

For its analysis, the agency used the raw data from the last observation and the first observation and adjusted for the time interval.

First, I'll show you the 12-month change in erosion scores using this new method of analysis. The

point estimate for Enbrel 25 milligrams was lower than that for methotrexate, and here the P value was .001. Again, the differences in the P value here compared to the ones I showed you before have to do with the different method of analysis, the nonparametric analysis, compared to the analysis of comparison of means.

Next, we looked at changes over time. First, I'll show you the data on erosions. You can see three things from this figure. First, Enbrel 25 milligrams shows less of an increase in erosion score in both periods, the zero to six months and the six to 12 months.

However, the differences between arms are more marked in the first period, even though the six-month rate of x-ray progression in the Enbrel arm is less in the last six months of the trial compared to the first six months.

The reason that the differences between the two arms is greater in the first six months is that there is considerably less x-ray progression in the methotrexate arm in the second part of the study.

The differences between the two arms are statistically significant in the first part of the study with a P value of .0006, and they were not significant in the second half of the study.

When this new method of analysis was applied to the total Sharp score for both periods as well as the total

12 months of the trial, similar results were seen. The point estimate for Enbrel 25 was lower for the zero- to six-month period and for the six- to 12-month period compared to methotrexate.

However, the differences between treatment arms were more marked in the first period, again primarily because the rate of progression for the methotrexate arm was considerably less in the second portion of the trial. Again, the differences were statistically significant for the first part but not for the second half of the trial.

Next, we looked at the proportion of patients who showed no radiographic progression, and I need to tell you here that the way we defined no radiographic progression was these were patients who had a change in the Sharp score of zero or less over the course of the trial.

You can see that the proportion of patients who had no radiographic progression during the 12 months of the trial in the Enbrel 25 milligram arm was higher than in the methotrexate arm, and this was statistically significant, a P value of .004. The differences in rate of progression using the total Sharp score were not statistically significant.

We also looked at subsets of patients for the degree of x-ray progression over the 12-month period, looking at the erosion scores. No important differences

were seen based on age, ethnicity, gender or duration of disease.

In addition, we assessed effects on radiographic progression based on baseline prognostic variables, and I'll show you data on patients with increased sed rate and patients with erosions at baseline.

In a group with elevated sed rate at baseline, and this is defined as a sed rate greater than 30 millimeters per hour, the increase in erosion score was less in the Enbrel arm compared to methotrexate in both the patients with elevated sed rate and those who had lower degrees in elevation of sed rate.

When patients were subdivided based on whether they had two erosions on baseline x-rays or less than two erosions, the increase in erosions was less in the Enbrel 25 milligram arm compared to methotrexate in both groups.

So in conclusion, although the trial excluded the prespecified margin for non-inferiority, there are limitations to the interpretation of these data.

Meaningful secondary endpoints did show a difference compared to the active control. For example, in erosion scores in the six-month data and in the proportion of patients who had no radiographic progression during the trial.

You've seen the clinical endpoint presented

already, and I'm not going to be talking about this in detail. We have no major disagreements with Immunex's interpretation of the data. I would just say that the primary endpoint of six-month area under the curve for the ACRn showed a statistically-significant difference between the Enbrel 25 milligram arm and methotrexate.

However, the landmark analysis of the proportion of subjects achieving an ACR20 and ACR50 at six and 12 months was not statistically significant.

Next, I'll show you data on the three other clinical endpoints, starting with disability.

The different treatment arms were balanced with the respect to degree of disability at baseline, and there were decreases in the level of disability as measured by changes in the HAQ in all treatment arms. The differences between arms was not statistically significant.

Quality of life was assessed using the SF36 Questionnaire. This was analyzed based on two summary scores, the physical summary score and the mental health summary score.

At baseline, the scores on the physical summary score were the same across treatment arms, and these were approximately two standard deviations below U.S. norms. The physical summary score improved in all treatment arms at 12 months. However, there was less improvement in the

10 milligram arm compared to the Enbrel 25 milligram arm.

The mental health summary score was similar to U.S. norms at baseline in all treatment arms, and these scores were higher in all treatment arms at 12 months, and the differences were not statistically significant.

Major clinical response was also measured. The major clinical response was introduced in the Rheumatoid Arthritis Guidance Document. The rationale for choosing a criterion of the ACR70 is shown here. The ACR70 represents a degree of improvement which is rarely seen in the placebo arms of controlled studies of disease-modifying agents.

For example, in one study of methotrexate versus placebo, no patients met an ACR70, and another study of cyclosporine A versus placebo in the context of background methotrexate, none of the subjects achieved an ACR70.

A major clinical response is defined as six consecutive months of an ACR70 with no measurement falling below an ACR70 response.

As you can see in this figure, a major clinical response was seen in some subjects in all three arms of the study. No statistically-significant difference was seen between treatment arms.

I'm going to be turning to the safety portion of the presentation. First, I'll cover serious adverse

events and deaths, patients who dropped out for adverse events, other adverse events, long-term safety, and, finally, the post-marketing reports.

Two deaths were observed during the 12-month study period. One of these was a subject in the 10 milligram Enbrel arm. The patient died of lung cancer approximately two months into the study.

The other subject was in the 25 milligram Enbrel arm, and this patient died of non-infectious complications of an aortic aneurysm repair.

The serious adverse events seen in the trial are shown in this slide, and I'll go through each of the first categories in more detail in the coming slides. The most common serious adverse events seen were infections, malignancies, thromboembolic events, and interstitial pneumonitis, and acute MI. There were no readily-apparent differences in the overall serious adverse event rates.

In terms of the infectious serious adverse events, pneumonia was seen in three patients in the methotrexate arm, one in the 10 milligram Enbrel, and three in the Enbrel 25 milligram arm, and the other infectious serious events are shown here.

You've heard about the malignancies from the Immunex presentation. Three malignancies were seen in the Enbrel 25 milligram arm, two in the Enbrel 10 milligram

arm, and one during the initial 12 months of the trial in the methotrexate arm. However, early at the beginning of the second year, an additional methotrexate patient developed bladder cancer.

The thrombotic serious adverse events are shown on this slide. Four events occurred, all of them in the two Enbrel arms. Two events were seen in the Enbrel 25 milligram arm. Both of these were deep vein thrombosis. One subject had a DVT following three months on study. The risk factor for this patient was taking oral contraceptive pills. Another subject developed a deep vein thrombosis one week into the study. They had a risk factor of Baker's cyst.

In the 10 milligram arm, there were two thromboembolic events seen, one DVT two weeks into the study. This patient had no risk factors, and, finally, one patient had a massive pulmonary embolus associated with the diagnosis of lung cancer.

Thromboembolic events were not seen in the previous randomized clinical trials. However, thromboembolic events have been reported post-marketing.

This table shows the number of subjects who did not complete 52 weeks of dosing. As you can see, a higher number of patients dropped out because of adverse events in the methotrexate arm compared to the Enbrel arm, and the

other reasons for dropping out are shown here. Similar numbers dropped out for lack of efficacy in the methotrexate arm and the Enbrel arm, Enbrel 25 milligram arm.

The adverse events leading to drop-out are shown here. One category is a set of adverse events which are associated with methotrexate use, including alopecia, oral and nasal ulcers and vomiting. Nine subjects dropped out in the methotrexate arm for these reasons. None in the two Enbrel arms.

The numbers for patients dropping out due to infection are shown here, 3, 3 and 1, malignancy. Methotrexate pneumonitis, there were three patients in the methotrexate arm, and none in the Enbrel arms, and this diagnosis was reached before unblinding of the patients.

Regarding laboratory values, the agency saw no significant patterns of abnormalities associated with the use of Enbrel.

In terms of other adverse events, overall, the adverse event rate was somewhat higher in the methotrexate arm compared to Enbrel. 95 percent compared to 90 percent. The rate of injection site reactions, the rate of bleeding at the injection site, were higher in the Enbrel arm than methotrexate, and these incidence rates were similar to that seen in other trials. No other pattern of increased

adverse events were observed with Enbrel.

I'll turn now to a discussion of long-term safety. In previous controlled studies, the only adverse event that was seen at a clearly higher rate was the rate of injection site reactions. However, in the long-term extension studies, some serious infections were seen, and along with the fact that the mechanism of action of Enbrel, namely blocking TNF, may impair an important arm of host offenses, it's very important to look at a number of things which are related to the immune system, including serious infections, over time.

At the time of the initial approval of Enbrel, Immunex agreed to do a Phase IV safety study, Study 16.0018. This is a three-year open-label study of 1,200 subjects receiving Enbrel, and most of these subjects are patients who were enrolled following completion of other clinical trials.

At the time of this BLA submission, 638 subjects were enrolled in the study, and the goals of this study are to assess long-term safety, including the mortality rate, the incidence of malignancy and autoimmune disease, compared to historical control databases.

The long-term safety data that I will be discussing with you includes 782 patients overall. Many of these are in the 16.0018 study but some of them are not yet

in that study, although they may roll over into this study at a later time.

There are 71 subjects who have been observed for two to three years on Enbrel, and 502 subjects who have been treated for a period of one to two years.

Overall, the adverse event rate showed no adverse events occurring with an incidence higher in the long-term safety study than was seen in the controlled studies, and no adverse event was seen with a pattern of increased incidence with longer duration of exposure.

Overall, the types of infections that were seen in the long-term safety studies were similar to that seen in the controlled studies, and no infection was seen with a higher incidence with longer duration of treatment.

Serious infections are defined here as infections associated with hospitalization or with use of IV antibiotics. These occurred at a rate of 5.5 cases per 100 patient-years, and the type of infections that were seen were those expected for patients with rheumatoid arthritis in this age group. No increase in the rate of serious infections was observed with longer durations of exposure to Enbrel.

In the six months following approval of Enbrel in November of 1998, cases of serious infection were reported on Enbrel to the agency. Of these cases, a number

of deaths occurred, approximately six cases of an estimated 25,000 patients who had been prescribed Enbrel.

A number of these cases occurred contemporaneously with beginning Enbrel, and review of the data indicated a pattern of potential risk factors, many of the patients having risk factors which may predispose to infection.

The agency felt that it was difficult to interpret these data. Of course, the data cannot be dismissed. However, it's difficult in view of the risk factors many of these patients had to attribute these serious infections with certainty to use of Enbrel. Therefore, it was thought important to do a number of things, including doing further studies.

So as a result of the review of these data, Immunex issued a Dear Doctor letter with a warning about the use of Enbrel in patients with potential risk factors for infection, namely patients with diabetes, active infections or with a history of chronic infections.

In addition, the agency asked Immunex to initiate a clinical trial to assess the degree of risk for patients who might be at risk of serious infections.

Again, as I said before, since the clinical trials excluded patients at higher risk for infection, it is unknown whether Enbrel may predispose certain subgroups

of patients to serious infections since many of these patient groups may not have been studied previously.

Study design is shown here. It's a 1,000-patient randomized four-month study, double-blinded placebo-controlled study, of Enbrel, and inclusion criteria for the trial is rheumatoid arthritis by ARA criteria, and one of these four potential risk factors for increased infection.

First, diabetes requiring insulin or oral hypoglycemic agents, chronic pulmonary disease, such as COPD or asthma, a history of pneumonia in the past year or a history of recurrent bronchitis, sinusitis or urinary tract infection with at least two episodes in the past year.

Immunex submitted the following sample size calculations. These sample size calculations assume an event rate of 10 percent in the control arm, and these are estimates since we don't know quite what the event rate will be in this patient population.

Based on these assumptions, the study has a 94 percent power to exclude a twofold relative risk for Enbrel using the 95 percent confidence interval. However, the power of the study would be lower if the event rate were actually less than 10 percent.

So finally, in conclusion, regarding the x-ray

data, the 95 percent confidence interval excluded an inferiority of Enbrel to the active control of 1.2 units per year. In addition, secondary endpoints suggested superiority of Enbrel in preventing erosions.

The primary signs and symptoms endpoint, the ACRn area under the curve, showed superiority for Enbrel 25 milligrams over the active control. However, the landmark 6- and 12-month ACR20 and 50 responses were higher for Enbrel 25 milligrams, but the differences were not statistically significant.

And in summary of the safety data, the overall adverse event rate and the serious adverse event rate were not measured to be higher with Enbrel than with methotrexate.

Thank you.

DR. ABRAMSON: Thank you, Dr. Siegel.

Perhaps if you don't mind staying there, and if a representative from the sponsor could come to the podium, what I'd like to do now is just have questions from the committee, but for this period really first restrict our questions to clarification of the data and the presentations as best we can.

So would someone like to comment? Janet?

DR. ELASHOFF: On Slide C-26, it said that an inclusion criteria was that people had to have at least

three erosions, but in Table 4.2D on page 43 of the briefing document, it showed a range of Sharp scores for erosions down to zero.

DR. GARRISON: Dr. Finck will answer that question.

DR. FINCK: They only had to show erosions on baseline x-rays if they were negative for rheumatoid factor at screening. So a person who did have a positive rheumatoid factor was not required to have erosions.

DR. ABRAMSON: Dr. Harris?

DR. HARRIS: Dr. Siegel, can you remind me about the definition from the FDA's prevention of erosions versus the slowing erosions? Are there some guidelines with respect to that?

DR. JEFFREY SIEGEL: Yes. I hadn't prepared for this, so I'll try my best to answer the question.

In the Rheumatoid Arthritis Guidance Document for making a claim of prevention of structural damage, several different ways of doing it were stated.

One is to show a difference between study drug and control in the rate of radiographic progression, but the other one, as you point out, was to show a difference in the proportion of patients who have new erosions, and I don't think it was spelled out exactly what this means.

One way that this could be shown is to show an

increase in the proportion of patients who have no new erosions whatsoever in their survey of joints.

DR. GARRISON: Jeff, we do have a slide on that that quotes your document.

DR. ABRAMSON: No. I'd prefer that we not -- just crisp answers right now.

Dr. Brandt?

DR. BRANDT: Yes. A question, please, with regard to malignancy, and I followed the incidence data that you presented.

Have there in fact been patients who were started on Enbrel who had a prior history of malignancy, and have all of the patients who were diagnosed with malignancy in the trials or post-marketing had Enbrel discontinued or have some patients with malignancy been continued on Enbrel, and what's happened?

DR. GARRISON: in the clinical trials, patients were excluded from entering the clinical trials if they had had a recent history of malignancy, but they were included if they had had a prior malignancy quite distant. So there were some patients in our original clinical trials who had treated breast cancer, et cetera.

We have had some patients in our trials who have elected to remain on Enbrel after their malignancy has been treated.

DR. BRANDT: Any comments on those? Any information on those?

DR. GARRISON: For these patients, it was a personal decision between their physician and the patients. They felt that their quality of life was far better on Enbrel therapy, and after receiving adequate treatment elected to stay on Enbrel, and at this point, I don't have any anecdotes on exactly how those patients are doing.

DR. ABRAMSON: I have one question regarding the rate of progression, the predicted rate of progression of placebo-treated patients.

The study that you referred to that modified the protocol was, I believe, the Rich study -- is that correct? -- that was in our document that showed methotrexate prevented progression compared to placebo? It was a Journal of Rheumatology article that was referred to.

The question I had in that group, what was the total Sharp score progression in the placebo that methotrexate did better than -- and I've forgotten the Arava database. I recall there was a placebo group in there.

So are you hitting this five- to six-unit per year in placebo in those two studies as opposed to the Wolfe study?

DR. JEFFREY SIEGEL: In the Arava studies that

were presented at the time of licensure of Arava, there were two placebo arms in two different trials.

In one of them, I believe the rate of progression was estimated as either 5.5 or 6 units per year. In the other study, the placebo arm was allowed to cross over into either methotrexate or leflunomide after a certain period of time. So this was not a purely untreated group, and their rate of progression was 2 units per year, but we don't know how long they were untreated for.

DR. ABRAMSON: Dr. Felson?

DR. FELSON: I have a couple of questions.

One relates to how the decision-making occurred in terms of changing the radiographic endpoint. The way you presented it, Jeff, was that you really initiated this discussion, and it sounded like the discussion was initiated pretty far into the trial, at a point when the company might have been privy to the actual rates they were seeing, and I wondered if you could comment on that, because that would have been a post-op change based on preliminary data, even though it turned out they probably should have held to the same primary endpoint that they started with.

The other question I have relates, I think, to the deep venous thrombosis pulmonary embolism issue, and you commented that in the open-label follow-up experience,

there are a number of cases of this.

I guess I would wonder, as the observed and expected rates for cancers were presented here, whether there are any data on the observed versus expected rates of DVT and pulmonary embolism that are available for this, and what they are, and also whether there's a biological mechanism that we can understand that might cause increased coagulation here.

DR. JEFFREY SIEGEL: Okay. You've asked a number of questions. I hope I have them all down.

In terms of the decision about changing the analysis of the radiographic endpoint, it is true, as you stated, that the agency initiated these discussions, and the reason was that the agency was concerned that when the trial was unblinded, that the active control arm, as I mentioned, might show so little radiographic progression, and we wanted to make sure that if Immunex was planning to use an analysis of non-inferiority, that that should be stated prospectively.

In terms of when that was decided, it's my recollection that that was quite early during the trial, although I can't remember exactly how many months in.

I'll need to ask Immunex to comment on the degree to which they were privy to the unblinded x-ray data.

DR. FINCK: We initiated discussions between the agency and Immunex probably about -- my best recollection is that it occurred about a year into the trial, when this data became available, and we were actually not privy at all to any x-ray results at that time.

The readers started reading after the patients had been in the study for about a year. They couldn't read until they had all three time points for a patient, and so although the readers started reading, Immunex was not privy to any kind of database until really just before we unblinded the trial when we started to receive data from bioimaging, but we had no ability to even look at their baseline scores at the time that we started talking about changing the analysis plan.

DR. JEFFREY SIEGEL: If that was an adequate answer to that question, I'll go on to the DVT.

I don't have incidence data on deep vein thrombosis and pulmonary embolus. Perhaps Immunex can make some more comments on that based on the historical controlled databases they've been looking at.

However, in terms of a biologic mechanism, these cases of thromboembolic events came as a surprise. They came initially on review of the post-marketing data that a small number of patients were reported who had deep

vein thrombosis a relatively short time following initiation of Enbrel.

Now, of course, when you're talking about 25,000 or 50,000 patients, that could have, of course, occur by chance, but it was noted, and then when it was looked to see whether that was part of this trial as well, we found the results shown here.

In terms of biologic mechanism, none has been proposed. We would be very interested in any comments from the panel about what parameters they think might be helpful to clarify this.

DR. GARRISON: If we could have the slide back up?

DR. ABRAMSON: I think it might be worth looking at -- urinary prostacyclin could be of interest here.

DR. GARRISON: We have done a little bit of research here, looking at the rates of DVT and pulmonary emboli in the general population and comparing that to what we've seen in our post-marketing safety surveillance program at this point. It's, of course, spontaneous adverse event-reporting data.

DR. ABRAMSON: First, Dr. Simon, then Dr. Pucino.

DR. SIMON: I have several questions, two of

which relate to safety, and one of which relates to efficacy.

The first question is, I was struck by the LFT abnormalities that were noted in the Enbrel-treated groups when previously, at a previous presentation, there was little evidence of LFT abnormalities.

The explanation offered that these patients were on non-steroidal anti-inflammatory drugs is an intriguing one. However, I presume they were on those drugs when they started the trial, and there must have been some noted baseline laboratory tests, whether they were elevated or not. So I assume that this was a crude elevation of LFT abnormalities which seems to be quite significant, although it's always minimized when you compare against methotrexate which is certainly more. I'm more interested in the biologic effect of what LFT abnormalities would be caused by in this circumstance.

My second question about safety is related to the lack of any evidence that you've presented about the generation of autoimmunity, and particularly as it relates to the DVT question.

Previously, there had been some evidence that there were spontaneous antibodies to various different things. You mentioned nothing in this data set about either measuring them or not, and there is a lot of perhaps

rumor in the community, in the rheumatology community, about the incidence of anticardiolipin antibodies, antinuclear antibodies and anti-DNA antibodies, and I wonder if you can comment on that, and then, after that, if I can ask the efficacy question.

DR. ABRAMSON: Okay. So there are two questions here at least. One is what do people think about the twofold elevations of the transonomisis in about the 20 percent of the patients, and the other is anticardiolipin antibody profiles, or antinuclear antibody profiles in these patients.

DR. GARRISON: We can put this slide up. This just is one that you saw in the presentation, which reviews the grade of laboratory abnormalities. These patients did have multiple laboratory tests over the entire year. This is the worst value that was ever observed, and these were primarily transient LFT abnormalities.

DR. ABRAMSON: And any new data on the auto-antibodies?

DR. GARRISON: The autoantibodies, Barbara.

DR. SILVER: In this trial, we not only measured autoantibodies, including antidouble-stranded DNA antibodies and anticardiolipin antibodies, at baseline, six months and 12 months, we did see fluctuations in the auto-antibodies in all of the autoantibodies, but we did not see

sustained elevations over multiple time period when we measured these.

The three patients who had DVT did not have anticardiolipin antibody present before or after those events.

We also in this trial looked at an autoimmune features checklist. It was special for this protocol. We were trying to evaluate whether there were treatment-emergent new autoimmune features, and if I could have that slide, please, the autoimmune features checklist did specifically try to look at signs and symptoms of lupus or overlaps, and there was no difference between the treatment groups, any of the treatment groups, with respect to the new occurrence of autoantibody feature or new autoimmune features, except for oral ulcers.

If we took out the term "oral ulcers," which, of course, are more frequent on patients with methotrexate, there was absolutely no difference, and there were no treatment-emergent autoimmune features.

DR. ABRAMSON: So just a clarification.

In the course of all the testing, the percentage of patients who ever had a positive auto-antibody comes into what range?

DR. FINCK: It's hard when you say any auto-antibody, but --

DR. ABRAMSON: Let's say anti-DNA antibodies.

DR. FINCK: Yes. Could I show this slide?

This is a baseline. It was not at any time, but as you can see, there were patients, about 1.5 to 2 percent of patients, who were antidouble-stranded DNA positive at baseline, and although the tests varied over each time we tested them, there were never times when patients had very high levels of the antidouble-stranded DNA. Most of the times, these were transient, and again you can see that there's variability, a little bit higher and a little bit lower, in the methotrexate groups but really not of very much significance.

DR. ABRAMSON: Dr. Pucino, and then Dr. Grant.

DR. PUCINO: Along the same line, in the open-label long-term follow-up studies, do we know anything more about autoimmune diseases occurring on Enbrel, and, also, what is the percentage of positive antibodies in that population?

DR. GARRISON: In the open-label long-term treatment trials, we've seen no cases of SLE. We have banked serum from these patients, and we have not retested them for the development of autoantibodies.

We did all of that very careful work using the controlled trials, looking specifically at the placebo groups, here with the methotrexate group, and we have that

sera available in case there does appear to be developing clinical symptoms, but at this point, there's no clinical symptomatology at all and no cases of SLE.

DR. ABRAMSON: We'll have one question from Dr. Simon, and then a final comment from Dr. Elashoff.

DR. SIMON: I just found it interesting that the ACR20, even the pictured area under the curve, and as compared to the ACRn, I was wondering if someone could explain to me exactly what was done. By doing the ACRn, why did it change the numbers the way it did, in that I understand the ACRn minimizes the various different measurements, and thus one can't do a cut on these various different measurements as you can with the traditional ACR area under the curve, and thus it might change the data in a spin way, thus perhaps giving us a better improvement than would be measured with the more traditional measurement, and since much of these data are turning on this particular measurement of the ACRn, a particular measurement that's not entirely well accepted by everyone in the rheumatologic community, and since I'm not a statistician, I was wondering if somebody with more experience in this area could comment on that.

DR. ABRAMSON: Right. May I suggest that it's an important issue? It actually is one of our major questions in the discussion period. So I think we'll get

into that in a lot of detail.

Dr. Elashoff is going to address some statistical issues that she thinks have an impact.

So thank you very much, and we'll have this presentation here.

DR. ELASHOFF: Is there a way to have the microphone and to point at my slides at the same time?

PARTICIPANT: Use the wireless microphone.

DR. ELASHOFF: Okay. Well, I'll just go ahead.

The comments I want to make are not so much ones that I think influence how we regard the results of this particular trial but I think, to the extent that it's setting policy for what we might do in future, this kind of definition of superiority and of not inferior can lead to extremely inconsistent kinds of results.

The top line there shows that if a benefit of new drug is positive or to the right, so that if that benefit as compared to the standard, the confidence interval excludes zero, then the drug would be called superior, and it doesn't have to exclude it by anything more than a fraction.

If you define, like in this case, a non-inferior cut point which is far away from zero, like 70 percent of the effect, you could have a confidence interval that satisfies the not-inferior criteria but still would be

markedly statistically inferior, and so I object to this kind of definition of using superiority one way and not inferior the other.

The second comment I wanted to make is there were talk about guessing what the progression rate would be for placebo or methotrexate, but there's no talk about where the 70 percent rule came from. Most equivalence or bioequivalence is done with 80 percent, and even then, I think those are frequently broader than one would like to have.

Also in this particular trial, and I guess mainly for historical reasons, we're in the situation of looking for non-inferiority for the sum of two scores, erosions plus joint-space narrowing, and looking for superiority on one of those two. So they're not really two different measurements. One is the sum of two measurements, and the other is that particular measurement.

So I would like to say that in terms of setting a precedent, I wouldn't like to see these particular definitions set a precedent.

Thank you.

DR. ABRAMSON: Thank you.

Yes?

DR. JAY SIEGEL: Just as a matter of clarification, I think many of us in the agency would not

like to see this set a precedent, and I thank you for your comments.

I do want to comment a little bit on this issue you raised of non-inferiority. It is in fact a poor choice of terms. It is in the International Harmonization literature and in the statistical literature, and we use it.. Some of us prefer not to, but in that an inferior drug can meet a non-inferiority standard, but it's important to note that there are two different goals of an equivalence trial or a non-inferiority trial, and they differ importantly from a regulatory perspective.

One goal is to prove that drugs are interchangeable, that the new drug is as good as, as useful as, the other one, and for that you may want to set a very high standard that it retains at least 70 percent, 80 percent, whatever number you choose, there's no magic well-accepted number, and in thrombolytics for mortality trials, 50 percent has been used.

But that involves a lot of pragmatic decisions as well as clinical decisions, but the other reason you can use a non-inferiority design is simply to prove that the new drug is effective, and by law and regulation, we do not require -- and I'm sure many members of this committee have observed this in the NSAIDs -- you do not necessarily require a new drug to be as good or almost as good as other

drugs. What you require of a new drug is that it be effective. So arguably, as long as you prove that you retain some of the benefit of another drug, even though you may be inferior, as Dr. Elashoff showed, you may well be effective, and we would not use a study of this design to allow a claim of equivalence or non-inferiority just to support a claim of efficacy. So that's a distinction I want to raise there.

I think one can argue a lot about whether 70 or 80 percent or 50 percent or what's the right number. I actually have more concerns about the number that we took that percent of before, but just so you understand, though, that we're not so much talking about using this to establish that it's non-inferior but, rather, to establish that it has activity, that it has efficacy.

DR. ABRAMSON: Thank you very much.

I think that's a good point to end this morning's session on.

We'll take a 15-minute break and reconvene at about 10:30.

(Recess.)

DR. ABRAMSON: We're now going to begin the open public hearing, and first hear from Judith Levinson.

MS. LEVINSON: Good morning, Mr. Chairman and Members of the Food and Drug Administration advisory

committee.

My name is Judith Levinson, and I appreciate this opportunity to address you today. Not being a professional speaker, please excuse me if I appear somewhat nervous.

I am 55 years old and have crippling rheumatoid arthritis for the past 15 years. I have undergone six surgeries on my feet, resulting in one inch bone loss to the length of each foot. Both my hands have also undergone six surgeries, including knuckle replacements, tendon transfers to my thumbs. My wrist bones were removed, and six inch rods were inserted making them stationary.

I'm sharing this information with you to give you background on my condition, and to tell you how Enbrel has given me back a quality of life that I did not think ever would be possible for me again.

I am a wife, a mother, a daughter, and a sister, a published poet, and have designed and worked with stained glass. My artisan name is Wounded Dove. Although rheumatoid arthritis has affected my physical condition, it has not taken control of my creative spirit.

If Enbrel had been available when I was first diagnosed, perhaps I would have been spared some or all the painful surgeries I have endured, and I would not have lost years of an active and productive life.

For the past 15 years, I have had to overcome enormous obstacles, becoming so disabled that I had to retire on disability in 1991. I was forced to give up many activities that I loved because of constant pain and swelling in my joints.

I was trapped in a body that could no longer bike-ride, ice-skate, play tennis or horseback ride. Holding a fork or using a knife to cut my food was almost impossible. Every day was a bad hair day because I was unable to raise my arms to comb my hair.

I needed help dressing because I could not pull a top over my head or button a button. These were the darkest days for me. I feared I would ultimately be confined to a wheelchair.

Rheumatoid arthritis attacks joints causing constant pain and swelling that can result in crippling and disfigurement. My hands are so misshapen, I am often stopped by total strangers and asked what is wrong with them.

A little over a year ago, my life was dramatically changed for the better. On January 7th, 1999, I came home from an appointment with Dr. Howard Levine, who is affiliated with the Center for Rheumatic Disease and has been in practice for over 30 years and for whom I have great respect and trust.

That day will forever be stamped in my memory because that is the day my life was returned to me. Enbrel became my miracle drug. I started my injections that day and to date, I have given myself a 132 shots. Enbrel can now prevent future destruction of my joints, although nothing can repair the damage that has already occurred.

Over the years, I have tried a gamut of drugs, many of which caused severe side effects, including fatigue, swollen joints, incredible pain and extreme depression.

Since I started injecting Enbrel, my strength and energy level has been restored. No side effects, only positive results.

I'm asking you to make Enbrel available to all who suffer from this debilitating and crippling disease, whether mild or severe. Do not let another person, young or old, suffer unnecessarily. You have the power to see that this does not have to happen to future generations by approving Enbrel for people facing a diagnosis of active rheumatoid arthritis.

I also want to take this opportunity to thank the Immunex Corporation family of scientists and employees who have spent the last 10 years researching and developing drugs like Enbrel.

You are my champions in the fight for a

disease-free world. There is a light now at the end of a very dark tunnel for me and for many other people. Your dedication to the science of providing drugs for medical treatment benefits all mankind and allows people to have a better quality of life.

Also, I'd like to thank the committee for approving Enbrel and changing lives of thousands of patients like myself.

Before Enbrel entered my life, I wrote the following poem, called "Wounded Dove's Final Song," which has been published, and I would like to share it with you.

"Many seasons and sunrise have come to pass, my soul grows tired and cold lasts. My song voice weak and low, I can no longer go this alone. The other songbirds come and watch as I try to stay upon my perch in the tree, which can no longer shield me from past injuries.

"When the final day has come, I pray some kind soul will find and bury me under my favorite poplar tree, so I can hear the songs of the other birds in the trees as they watch over my soul and remember me."

Thank you.

DR. ABRAMSON: Thank you, Ms. Levinson. We appreciate your comments. We are all very impressed by the courage of people like yourself with rheumatoid arthritis.

Norine Walker?

MS. WALKER: Good morning, ladies and gentlemen.

I'm an individual with rheumatoid arthritis, and I don't have any financial interests in Immunex Corporation.

I was here a couple of years ago when the panel was considering the approval of Enbrel and was moved by the speakers prior to my own presentation that had been involved in the clinical trials, I had not, and particularly moved by one of the women that said that prior to having met Enbrel, she had not been able to raise her hand to brush or comb her hair. We've all been there.

And also remembering how fortunate I had been that I had been diagnosed early with the onset of the disease only four months after the symptoms had started and had been treated in a team approach by physicians and other care-givers.

When I was diagnosed by a rheumatologist locally in a teaching institution, the first thing that he told me was that in five years, typically, people with rheumatoid arthritis are disabled, not something that someone who's 18 years old wants to hear, when they're ready to start their college career and set the world on fire.

But I started with the treatments for

rheumatoid arthritis, and as I moved from my college days at the University of Maryland up to my professional career in Baltimore was treated by a Hopkins-trained rheumatologist, but not only the medicines that she scripted for me, but she also scripted treatment with physical therapists, with hand specialists, with foot specialists, and over time, as the disease progressed, the interaction of the drugs continued to progress, led me to my team of cardiologists, psychologists, internists, gastroenterologists, et cetera, et cetera, as many of us that have rheumatoid arthritis have to travel with this disease.

One of the things that I have found through meeting some of the other people with rheumatoid arthritis is the great impact that Enbrel has had on some of them. Of the 43 million Americans, I fortunately have met a handful of them. Some of them are young adults similar to myself that have had such terrific benefits from being on Enbrel as I have. Something simple as being able to participate in athletic sports, not competitively maybe but being able to have a regular exercise program, being able to downhill ski after not having had that chance for many years.

Even my friend that's able to lift her hands above her head and reach the back of her head, which she

hadn't been able to do for years and years because, as a three-year old diagnosed with rheumatoid arthritis, she had severe limitations.

We've suffered with side effects of medicines. We've suffered with doctors' visits, with lab tests, with contraindications, with complications, as I've mentioned, with the rheumatoid arthritis drugs, triggering other maladies, but we've gone through these travails with our arsenal of medicines, and as we've started to be treated by Enbrel, we've seen opportunities to reduce that arsenal.

Fortunately, my epiphany came earlier this year when, after having done my morning routine of range of motion exercises, I was able to sit on the end of my bed before I got ready for work and say I have no pain, I have no pain. There is no pain.

For somebody that's had this for 20 years, to have that epiphany, that light bulb go on, is quite astounding. Now, I don't have those days every day, but they're increasing in number, and I've been able to start tapering off some of the other medicines that I'm on.

My hope is that in the future, that I may be on only one or two of these medicines rather than my full grouping, and that is encouraging.

However, there are people out there that are not yet at the moderate to severe rheumatoid arthritis that

I and some of my young adult friends are, who need to not go through 20 years of medicine, side effects, complications, surgeries, visits to labs, visits to physical therapists.

For early intervention, and I feel as if I had early intervention because I had a team of professionals that were looking out for me. I think that that's very, very valuable.

My quality of life having had the early intervention was improved remarkably. I've been successful professionally and have contributed to society, and that's what I could see from Enbrel being used for early treatment in persons with arthritis. They won't have to suffer through the things that we have and won't have to be debilitated or be on the disability rolls.

The impact of having reduced the disability rolls by people with rheumatoid arthritis is something to be thought about.

My remarks a couple of years ago also included the encouragement to continue with trials of individuals such as myself that have other complications beyond simply rheumatoid arthritis, and I think that comment was obviously taken to heart to a certain extent because we are looking at it for early treatment, but there are still cases where the research needs to continue, so that the

medicines that we are providing are safe and have minimal side effects.

Thank you.

DR. ABRAMSON: Thank you.

Gloria Brennan?

MS. BRENNAN: Good morning, everyone.

Like Judith and Norine, I, too, have rheumatoid arthritis, and this morning, I feel extremely grateful, extremely blessed and really humbled by the fact that I was diagnosed in May of 1997, and Judith and Norine had a lot more pain, a lot more stiffness, and if anyone has been there, you just want to cry for them because my experience with it was so short when compared to theirs.

Anyway, I want to tell you I'm very spontaneous the way I speak. I try to be organized, but it never works out. So forgive me for that.

I took a bath this morning, and I was thinking of all the things that I so took for granted before rheumatoid arthritis ripped my life apart. I took a bath, and I watched myself taking a bath and watched myself lift my body off the tub with my wrists, and I thought that was pretty good, you know, when I think about the other way I was.

I played tennis the other day, very poorly, but I bought myself a new racket. I always wanted one, and I'm

a bad player, but I played, and I ran with my dog and walked with my dog Ginger, my Australian shepherd that I found a couple of years ago. She's a big dog. I don't like big dogs, but I'm stuck with her. She can run and knock me down, but now I have the freedom and the energy to do lots of things.

I live in Owings Mills, Maryland. I have a full service salon and a day spa at the Hilton in Pikesville. I'm from Colombia, South America. My mother is here with me, and when I first got diagnosed with rheumatoid arthritis, all I could envision was twisted fingers and pain because a girl in my chorus in church at the time had it, and she always wore slippers, and she always walked real slow.

So when I first got it, I went into an immediate denial about it because I didn't have any real pain. I just had inflamed joints in my wrists only. I mean right here, the telephone finger joints.

I went to the library. In fact, I didn't tell my mother about it. I didn't want to upset her. I went to the library and got all the books on rheumatoid arthritis, so that I could read about what was in store for me, and at this point, I had not had any flare-ups. I didn't know what was going to come, but what I read was very, very negative. It was like, okay, you have it, here's what you

can expect the first six months and the next six months, and within two years, it will be possibly total joint destruction.

I'm single, I have my own business, and I'm in the business of making people feel and look good, and therefore I did not like what was going to be in store for me.

I remember calling my -- I didn't even know a rheumatologist. Since then, by the way, I did date one, but our joints didn't connect.

(Laughter.)

MS. BRENNAN: And I learned about Arava, too, in that dating process.

(Laughter.)

MS. BRENNAN: And at an Arava meeting, I stood up. I didn't know it was an Arava meeting because I didn't know what Arava was, but it was like 350 rheumatologists, and I was so excited about Enbrel, I just had to share it, and I did, and the rheumatologist that I was with, he said, "That was not politically correct," and then somebody from Arava said, "You'll have to pay for your own dinner."

(Laughter.)

MS. BRENNAN: So you know, needless to say, we didn't last very long.

So the rheumatologists at Sinai Hospital in

Baltimore recommended some drastic aggressive measures. My mother went with me because I had to wait three weeks for that meeting, and it came on, the flares came on, slowing walking, no heels, I have heels today, flat shoes until my study, and nothing really worked. That's the thing that really upset me because I would get upset stomachs, but nothing seemed to work.

I remember going to Ocean City one time in Maryland to just relax, and I had a flare-up, and I really love swimming. I wanted to go into the ocean, and I couldn't. I had to ask people to help me walk into the ocean, knee length, knee deep, and I couldn't bend.

So I agree that Enbrel should be a drug recommended for an early diagnostic of rheumatoid arthritis simply because from what I've seen today, it stops the progression and the destruction of the joints, and we all need our joints to stay mobile and to have a full quality of life.

Thank you, Immunex. You gave me back my life. Thank you, FDA. Go for it.

DR. ABRAMSON: Thank you very much.

It is our hope that we develop drugs that can make people better, everyone better, who takes them.

Dr. Klippel from the National Arthritis Foundation.

DR. KLIPPEL: Good morning. My name is Jack Klippel. I'm a rheumatologist and medical director of the Arthritis Foundation.

It's indeed a privilege and a bit of a humbling experience to follow patients to the microphone, particularly those who have benefitted from such a major advance, and I should say on a personal level, that in two of the instances, for Judy Levinson, who more than a decade ago I saw in the first year of her illness, and neither of us had a clue what was in store for her, and I've lived through years where she suffered greatly and am particularly gratified that she's happy and doing well, and I have the privilege of working with Norine Walker, who is in fact a leader in the Arthritis Foundation and whose leadership is actually responsible for many of the things that occur within the Foundation.

I speak today as a representative of the Foundation, to comment on the major advances in the treatment of rheumatoid arthritis that have occurred over the past decade.

A longstanding era of empirical therapy has given way to scientifically-based treatments that in a short period of time has resulted in dramatic improvements in the lives of people affected by this chronic, disabling disease.