FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

ARTHRITIS ADVISORY COMMITTEE

8:07 a.m

Tuesday, June 24, 2003

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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WILLIAM TAUBER, M.D.
MARC WALTON, M.D.
KAREN WEISS, M.D.

ATTENDEES (Continued)

AMGEN REPRESENTATIVES:

DANIEL BURGE, M.D.
WAYNE TSUJI, M.D.
DESIREE VAN DER HEIJDE, M.D.

ALSO PRESENT:

JANE BRUCKEL
JASON CRISPIN

C O N T E N T S

Enbrel
Indicated for the Treatment of Ankylosing Spondylitis

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P R O C E E D I N G S

8:07 a.m.

DR. WILLIAMS: We welcome you all to this advisory committee meeting today. We would like to start off by introducing the committee. We'll have them introduce themselves.

Fred, if we could start with you, and we'll move around.

DR. LASKY: Fred Lasky. I'm the Director of Regulatory Affairs for Genzyme. I'm the acting industry representative.

DR. ANDERSON: Jennifer Anderson. I'm a statistician from Boston University.

DR. FINLEY: Michael Finley. I'm a rheumatologist from Western University.

DR. FRIES: Jim Fries, rheumatologist from Stanford.

DR. WILLIAMS: Jim Williams, rheumatologist, University of Utah.

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

DR. HOFFMAN: Gary Hoffman, rheumatologist, Cleveland Clinic.

MS. McBRAIR: Wendy McBrair, Director of Arthritis Services, Virtua Health, in New Jersey, consumer

rep.

DR. VASEY: Frank Vasey, rheumatologist from the University of South Florida in Tampa.

DR. SIEGEL: Jeffrey Siegel, Acting Branch Chief, Immunology and Infectious Diseases Branch, FDA.

DR. TAUBER: Bill Tauber, also of the Clinical Trials Division of the FDA.

DR. WILLIAMS: Thank you.

We'll now turn the podium over to Johanna Clifford for our conflict of interest statement.

MS. CLIFFORD: Thank you.

The following announcement addresses conflict of interest issues with respect to this meeting and is made a part of the record to preclude even the appearance of impropriety at this meeting.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their own or their employer's financial interests. All participants have been screened for conflicts of interest in the product, competing products, and firms that could be affected in today's discussions.

In accordance with 18 United States Code, section 208(b)(3), the Food and Drug Administration has granted waivers to the following individuals because the agency has determined that the need for their services

outweighs the potential for a conflict of interest.

Dr. James Williams' waiver is for his participation on a competitor's Speaker's Bureau. He lectures on topics unrelated to today's discussions and receives between $10,001 to $50,000 a year. Also waived is his employer's interest in the sponsor of Enbrel. His employer is participating in two trials of Enbrel for ankylosing spondylitis and the total funding provided is less than $100,000 a year. Dr. Williams has no involvement in the studies.

Dr. Gary Hoffman's waiver is for his consulting for two companies, the co-marketer of Enbrel and a competing company. He consults on unrelated matters and receives less than $10,000 per year, per company.

Dr. Michael Finley has been granted a limited waiver for his participation on a Speaker's Bureau for a firm that co-markets Enbrel and that makes competing products. He lectures on topics unrelated to Enbrel and receives less than $10,000 annually. Under the terms of the limited waiver, Dr. Finley will be permitted to be participate in the committee's discussions. However, he is excluded from voting.

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

We would also like to disclose that Dr. Fred Lasky is participating as a non-voting industry rep, acting on behalf of regulated industry. He is a full-time employee of Genzyme and has a sales relationship with Wyeth. In addition, he would like to disclose that he owns a nominal amount of stock in Johnson & Johnson.

In the event the discussions involve any other products of 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.

In addition, letters were submitted to the FDA on behalf of Enbrel. They are available for public reading at the information desk in the lobby.

Thank you.

DR. WILLIAMS: The discussion today is on Enbrel and its indication for the treatment of ankylosing spondylitis, and the first presentation will be by Amgen and that will be led by Dr. Daniel Burge, Vice President of Clinical Research for Amgen.

Dr. Burge?

DR. BURGE: Good morning.

Members of the committee, the FDA, ladies and gentlemen, it is a pleasure to be here today to once again discuss the benefits of etanercept. As you're all aware, etanercept is established as an important therapy for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis. As ankylosing spondylitis is a disease with limited treatment options, it is exciting today to present to you the compelling results of the etanercept clinical trials.

After a brief description of etanercept in ankylosing spondylitis, Dr. Desiree van der Heijde, Professor of Rheumatology from Maastricht, Netherlands, will provide some insight into metrics in ankylosing spondylitis. Dr. Tsuji will then describe the AS clinical program and study results. I will conclude by presenting some data from the broader etanercept experience and a risk-benefit assessment.

Two consultants have graciously agreed to be with us here today. Dr. van der Heijde from the Netherlands and Dr. Clegg from the University of Utah.

As I believe most of you know, etanercept is a fully human TNF receptor attached to the FC portion of a fully human immunoglobulin molecule. As such, it is the

only marketed TNF product that utilizes receptor-binding specificity. Etanercept binds both soluble and cell-bound TNF with high affinity, thus making TNF biologically unavailable for interaction with cell-bound receptors. The human protein has low immunogenicity and no neutralizing anti-etanercept antibodies have been detected. Etanercept does not activate complement, nor initiate complement-mediated cell lysis. The pharmacokinetics of etanercept are well characterized with a half-life of 3 to 4 days and a narrow range of peak-to-trough concentrations. We believe that these product attributes are relevant to the etanercept efficacy and safety profiles.

Amgen has been a leader in the development of innovative therapeutics, such as etanercept. In November of 1998, etanercept became the first biologic approved for the treatment of patients with rheumatoid arthritis, dramatically improving patient care and raising treatment expectations for patients and clinicians.

In May 1999, etanercept became the first biologic approved for the treatment of children with juvenile rheumatoid arthritis and it remains the only biologic approved for this indication.

In June of 2000, etanercept became the only biologic approved as the first-line therapy for rheumatoid arthritis and the first biologic approved for the

inhibition of radiographic progression of disease.

In January of 2002, etanercept became the first disease-modifying therapeutic, biologic or small molecule, approved for the treatment of psoriatic arthritis. Evidence demonstrating that etanercept inhibits radiographic progression in patients with psoriatic arthritis was submitted to the FDA for review late last year.

In January of this year, we submitted the application under review today. Etanercept is the first agent, other than non-steroidal anti-inflammatory agents, to be reviewed by the FDA for approval for patients suffering with ankylosing spondylitis.

Ankylosing spondylitis is the prototypic disorder in the group of disorders referred to as spondyloarthropathies. Reactive arthritis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, juvenile chronic arthritis, and undifferentiated spondyloarthropathies are other members of this group. The features common to all of these disorders define ankylosing spondylitis.

Sacroiliitis, with or without spine involvement, is the hallmark of the spondyloarthropathies. Enthesitis, inflammation of the attachments of tendons and ligaments in bone, is also characteristic. Peripheral

arthritis is variable and is classically oligoarticular. Anterior uveitis occurs commonly. Rheumatoid factor is not associated with ankylosing spondylitis while the genetic marker HLA-B27 has a high prevalence.

Ankylosing spondylitis is the most common spondyloarthropathy and represents approximately 350,000 individuals in the United States. The age of onset is typically in the 20s and 30s and almost always prior to the age of 45, though the diagnosis may be delayed beyond this age. Men are more commonly affected than women and typically have more severe disease. Inflammatory back pain, usually with insidious onset, is characterized by prolonged morning stiffness and improvement with activity.

As the disease typically begins in early adulthood, it may progress over many decades. Inflammation and fusion of the sacroiliac joint occurs, followed by an ascending ankylosis of the spine. Classically, the spine will fuse with a degree of kyphosis of the thoracic spine with the head thrust forward. Hip disease and flexion contractures of the hip contribute to the appearance in advanced disease. Gradually, as mobility is lost, affected individuals may be unable to turn their head or lie down flat.

For decades, the primary therapy for ankylosing spondylitis has been physical therapy to maintain motion

and non-steroidal anti-inflammatory drugs to relieve pain and stiffness. Unfortunately for many patients, pain relief provided by NSAIDs remains unsatisfactory. Additionally, NSAIDs have had limited effect on spinal mobility and systemic markers of inflammation.

Other therapies, primarily extrapolated from the rheumatoid arthritis armamentarium, have been utilized. Corticosteroids provide limited benefits and have significant toxicities.

Multiple studies have been performed with sulfasalazine in ankylosing spondylitis and though the results are mixed, sulfasalazine does seem to have effect on peripheral arthritis but not for axial disease.

Methotrexate has been less well studied but also does not seem to provide benefit for spine disease.

Other agents have primarily been used anecdotally as there have been no well-controlled studies.

During the 1990s, the importance of TNF in the pathophysiology of spondyloarthropathies became apparent. TNF levels were demonstrated to be elevated in the serum and in synovial tissue of patients with ankylosing spondylitis. This photograph depicts staining of messenger RNA for TNF in tissue from the sacroiliac joint of a patient with ankylosing spondylitis.

A challenge of designing a clinical trial for

the treatment of ankylosing spondylitis is that this condition has many manifestations, including pain and stiffness, disability, decreased spinal mobility, and decreased quality of life. There are many instruments that exist that may be used to assess these different aspects of disease activity in ankylosing spondylitis and there is no general consensus of which measure should be utilized as the primary response measure.

I would now like to introduce Dr. Desiree van der Heijde, Professor of Rheumatology from the University of Maastricht. Dr. van der Heijde, along with a number of other clinical experts, has been addressing the issue of clinical response measures in AS for a number of years now. She will share with you some of the work this group has done.

Dr. van der Heijde?

DR. van der HEIJDE: Thank you, Dr. Burge.

I would like to introduce you to the Assessment in Ankylosing Spondylitis Working Group, or ASAS. This is a group of over 60 experts working in the field of ankylosing spondylitis, including rheumatologists, clinical epidemiologists, and patients. It's representing over 20 countries. It first started to work in 1995 because in the literature, we found that over 120 instruments were used to assess ankylosing spondylitis, and we tried to make a more

complete set out of that.

The mission statement of ankylosing spondylitis is to support and promote the study of ankylosing spondylitis, and this includes the increasing awareness and early diagnosis of the disease, the development and assessment and validation of assessment tools, as well as the evaluation of treatment modalities in order to promote clinical research with the ultimate goal to improve outcome of the disease, and it will be on the second topic that I want to discuss some issues with you.

First, we developed core sets for the assessments in clinical trials, and we decided to have three different core sets for three different settings. The first one is to assess symptom modifying anti-rheumatic drugs and physical therapy and they are supposed to have an effect on signs and symptoms. The second group is on disease controlling anti-rheumatic therapy. In addition to an effect on signs and symptoms, there should also be an effect on physical function/disability and lastly also on structural damage. And the last set is on the use for clinical record keeping or observational studies.

First, we decided to define the domains for each of these settings. So in the middle, you see the domains that are included in all three settings, and each circle gives the additional domains assessed for that

specific setting.

Here, I'll present to you the core set for the symptom modifying anti-rheumatoid drugs. In the left column, you see the domains, and in the right column, you see the instruments for each domain.

The first is the function and usually the Bath Ankylosing Spondylitis Functional Index is used for this, the BASFI.

The second is pain and there are two measures to assess pain. One is the overall pain due to ankylosing spondylitis and the second one is the pain during night, again due to ankylosing spondylitis.

For the domain spinal mobility, there are four different instruments: the first, chest expansion, modified Schober, and also occiput to wall. And in the later update of the core set, we added the lateral spinal flexion or the Bath Ankylosing Spondylitis Metrology Index, which is a combined score of several measures, one of them being the lateral spinal flexion.

Another domain is the patient global and this is assessed on the VAS.

Stiffness, usually the duration of morning stiffness but also the average of duration and severity of morning stiffness can be used.

And the final domain which was added also at a

later stage is fatigue, and here we use the question, the first question of the Bath Ankylosing Spondylitis Disease Activity Index on fatigue.

There are three additional domains, if we want to assess disease controlling anti-rheumatic therapy. That's the joints and those are assessed in 44 swollen joint counts and also the enthesis and you can use a validated enthesitis score for this. For acute phase reactants, ESR has been selected but also CRP can be used, and finally, x-rays of the AP and lateral lumbar spine, the lateral cervical spine, and the pelvis are advised to use.

I showed you that you could measure all these instruments with the visual analog scale that's shown here at the bottom, but it can also be assessed by a numerical rating scale and an example is on the slide.

A frequently used instrument is the Bath Ankylosing Spondylitis Disease Activity Index, and this has in total five different domains on fatigue, pain in neck, hips and back, pain and swelling in the other joints, sides painful by pressure and it's meant to assess enthesitis here, and two questions on morning stiffness. There's first an average of the questions on morning stiffness and thereafter there's an average of the five. Here, it's expressed from a range from 0 to 10. The visual analog scale can be assessed in centimeters going from 0 to 10 or

in millimeters, giving a range from 0 to 100.

After we set the core set domains and instruments, we decided that it would be important to have also response criteria compared to the ACR response criteria in rheumatoid arthritis. We decided to have the same domains included in the SMARD core set. So these are the patient global, pain, function, and stiffness, and all of these are included. We also tried to include the domain spinal mobility, but there was a fairly low responsiveness in trials with NSAIDs, so that was not included.

First, the most reliable and sensitive instruments were defined, and then we constructed a complete list of possible improvement definitions. Those were tested in two-thirds of the database and validated in the remaining one-third. It was statistically based on the discrimination between NSAIDs and placebo treatment, and later on, it was validated by both a Delphi exercise by the ASAS Working Group but also by end-of-trial judgments by both patients and physicians.

It was done in five randomized NSAID-placebo-controlled trials, included a large number of patients. It was short-term trials with a flare design and patients only with axial disease were included.

And these were the criteria that came out. These are called now the ASAS 20 improvement criteria. So

what we have is the four domains, patient global, pain, function, and stiffness, and the patient is called a responder if there is 20 percent improvement and the minimum of 10 units on a 0 to 100 scale in at least three of the four domains, and if the fourth domain is not included, there should be no worsening in that remaining domain of the same magnitude, and these are used now as endpoints in clinical trials.

In that large database, they performed as follows. The NSAIDs showed 49 percent of the patients had a response, and in the placebo group, 24 percent of the patients showed a response. But this is in trials with a flare design, and I will come back to that later.

When we validated that later on, it came out that the criteria are highly specific but not that sensitive. So that means that if patients show a response according to the ASAS 20 response, there is indeed improvement.

I want to address some caveats, if we want to compare the response rates obtained in NSAID trials and trials with anti-TNF therapy. Usually in NSAIDs trials, there's a flare design. I mentioned that earlier. That means that patients are on stable and safe treatment. They stop the drug. Then they get a flare and only if they get a flare that's large enough, they're able to enter the

trial and then they get the same NSAIDs sometimes or a different NSAIDs. That's completely different from anti-TNF trials. That's not a flare design. Patients are usually on stable NSAID treatment but they are not responding. Despite the NSAID treatment, they have a high disease activity, and then, in addition to that, they start with anti-TNF therapy. So the patients entered in NSAIDs trials have a proven efficacy of NSAIDs, and the patients that enter anti-TNF trials have a proven inefficacy of NSAIDs. And in the NSAIDs trials, we usually have inclusion of patients with mild to severe disease and in anti-TNF therapy trials usually severe disease.

That brings me to a different subject. First, I talked about improvements, so to see if the patient shows an effect, but it's also important to know how the patient is at the end of the trial, if the patient is really in a good condition, and to define that, the partial remission criteria have been defined. The patient is fulfilling this if there's a value below 20 on the 0 to 100 scale in all four domains.

Those ASAS 20 improvement criteria are based on NSAIDs trials, and the question is if it's valuable to assess also anti-TNF therapy trials with the same criteria?

In the ASAS Working Group, we decided to add two domains included in the DCART core set and not included

in the SMARD, and we compared that with existing ASAS criteria in a large number of combinations and also with improvement with various cut-offs in BASDAI. The extra domains that could be chosen from were the joints, but they show a very low responsiveness and it's only a small number of patients who have swollen joints at the beginning of the trial. The entheses, the instruments to assess that are still in the validation and therefore these two were not used. So the two domains included are spinal mobility and acute phase reactants. Radiographs to assess structural damage is a completely different aspect, so it's not considered here.

These response criteria are developed in one clinical trial and validated in other data sets and thereafter there was an opinion-based final selection by the ASAS Working Group members. These are the two definitions that came out.

The first one is ASAS 40 percent and 20 units of improvement, and you see these are on the same four domains as included in the ASAS 20, and there again also should be no worsening in the fourth domain.

The second set is a 20 percent improvement in five out of six criteria, including these two additional domains. These two sets need further validation and that will be done when new data become available.

Now, Dr. Tsuji will continue with the presentation of the clinical program and results.

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

Members of the committee, representatives of the FDA, ladies and gentlemen, I'm pleased to share the results of the etanercept clinical development program in ankylosing spondylitis.

The objectives of the AS development program were to establish the safety and efficacy of etanercept in AS, thereby confirming the role of TNF in the pathophysiology of AS.

401 subjects were studied in this development program. The program, consisting of three studies, began with a proof-of-principle study 16.0626, an investigator-initiated study with 40 subjects. Two larger studies comprised the pivotal program. The primary study was Amgen Study 16.0037. This multicenter study in Europe and North America included 277 subjects. A shorter supportive clinical trial, Wyeth's study 47687, included 84 subjects at 14 European sites.

The initiating proof-of-principle study was conducted by Dr. John Davis and colleagues at the University of California, San Francisco. This study suggested that etanercept would be a valuable therapy in ankylosing spondylitis. The results were published in the

New England Journal of Medicine in May 2002.

This was a randomized, double-blind study. 40 subjects with ankylosing spondylitis diagnosed by modified New York criteria with active disease enrolled in the study of etanercept, 25 milligrams BIW, versus placebo. Subjects were allowed to continue stable background treatment with NSAIDs, corticosteroids, and/or DMARDs. Subjects with psoriasis, inflammatory bowel disease, and reactive arthritis were excluded. Subjects with a positive rheumatoid factor or previously treated with TNF inhibitors were also excluded.

It should be noted that the UCSF study commenced prior to the development of the ASAS response criteria.

The primary endpoint of this study was defined by 20 percent improvement in three of five parameters with no worsening in the remaining two. The parameters included in the UCSF response criteria are listed here. Improvement in either nocturnal spinal pain or morning stiffness was required.

This study provided the first evidence that etanercept was effective in ankylosing spondylitis. Response was detected by week 4, the earliest time point. As can be observed, improvement at week 16, the primary endpoint, was highly significant.

Following the positive results of the Davis study, the pivotal program was launched by Amgen and Wyeth. The pivotal program consisted of study 16.0037 and study 47687. These randomized, double-blind, multicenter studies of placebo versus etanercept, 25 milligrams BIW, were nearly identical in design, differing only in duration. 277 subjects in the primary study were treated for 24 weeks, 84 subjects in the supportive study were treated for 12 weeks. Both studies required a diagnosis of definite AS by modified New York criteria and the presence of active disease. Stable background NSAIDs and prednisone less than or equal to 10 milligrams daily were permitted. Subjects were allowed to continue on stable hydroxychloroquine, sulfasalazine, or methotrexate and were enrolled with stratification for DMARD use. Since one of the important evaluations is impact on spinal mobility, subjects with complete fusion of the spine were excluded.

In contrast to the proof-of-principle study, the pivotal program studied a broad range of subjects, including those with associated psoriasis, inflammatory bowel disease, and reactive arthritis.

The primary endpoint for both studies was the ASAS 20 at week 12. The protocol-defined endpoint differed slightly from the ASAS response criteria published by Anderson in 2001 and discussed by Dr. van der Heijde. For

the domain pain, the protocol-defined ASAS 20 used the average of total spinal pain and nocturnal spinal pain while the ASAS Working Group specified total spinal pain only.

In the primary study, a conditional primary endpoint was the ASAS 20 at week 24 to be assessed if the earlier primary endpoint was achieved.

Additional endpoints are listed here. Higher levels of response were assessed. The ASAS 50 and 70. The low disease state of partial remission and DCART responses by ASAS-proposed criteria discussed by Dr. van der Heijde were also assessed. Pain, stiffness, patient function, and patient global self-assessment, all patient-reported outcomes, and elements of the ASAS response criteria were determined.

Importantly, we assessed spinal mobility by modified Schober's test and by measurements of chest expansion and occiput-to-wall distance. Acute phase reactants, measures of the systemic inflammatory response, were determined. Finally, peripheral joint counts were performed.

Baseline demographic characteristics of subjects in the placebo and etanercept groups were generally well balanced. Mean age was approximately 42 in both studies. As expected, males predominated. Mean

duration of disease was approximately 10 years. In the supportive study, etanercept subjects were slightly older and had mean duration of disease of 15 years. This slight imbalance did not affect the outcome. Subjects were predominantly caucasian. As expected, approximately 85 percent of subjects had a positive HLA-B27, a genetic marker highly associated with ankylosing spondylitis.

Close to 90 percent of subjects had received NSAIDs and approximately 15 percent of subjects had received corticosteroids within 6 months of baseline. Between 30 and 40 percent of subjects were on DMARDs, the most common of which were sulfasalazine and methotrexate.

In both studies, baseline disease activity was balanced between treatment groups. As you are aware, all measures are on a 0 to 100 scale. Also note that subjects had active disease defined by stiffness of 30 or higher and scores of at least 30 in two of the remaining three measures listed.

Completion at the primary endpoint was high. In fact, 96 percent or better. By week 24, in the primary study, the most common reason for discontinuation in the placebo group was lack of efficacy. I will discuss discontinuations due to adverse events later in the presentation.

The primary endpoint in both studies was

achieved. ASAS response at week 12 in the primary study was confirmed in the supportive study. Response rates for the Anderson-defined ASAS 20 were nearly identical at this and every other time point. Improvement with etanercept was rapid and significant, seen as early as 2 weeks, the first assessment after start of treatment. Improvement was maximal by 8 weeks and sustained to 24 weeks, the end of the study. Clinical response to etanercept was highly significant at all time points.

Higher levels of response, the ASAS 50 and 70, were achieved in a greater proportion of patients treated with etanercept than placebo. These differences were highly significant in the primary study. These responses were also observed in the supportive study.

The low disease state of partial remission discussed by Dr. van der Heijde was achieved by significantly more subjects on etanercept in the primary study. To remind you, partial remission is defined as a score of less than 20 in each of the ASAS criteria. The same trend was observed in the supportive study.

The ASAS Working Group proposed response criteria for disease-controlling anti-rheumatic therapies. Significant responses by DCART 20 and DCART 40 were observed at weeks 12 and 24 in both studies.

Greater improvement was seen in all of the

individual elements of the ASAS 20 with etanercept in both studies. As you can see, there was significant improvement in subject global scores, pain scores, the Bath Ankylosing Spondylitis Functional Index and in the stiffness questions from the BASDAI. Note the consistency of results.

Limitation of spinal mobility is a hallmark of ankylosing spondylitis. Traditional therapies have not consistently or significantly improved spinal mobility. We found significant improvement in all three spinal mobility measures in the primary study at weeks 12 and 24, including Schober's test, chest expansion, and occiput-to-wall distance. Note the improvement between weeks 12 and 24. For occiput-to-wall distance, mean improvement at 24 weeks exceeded 1 centimeter. Improvement was also observed in the supportive study.

Typically, peripheral joint involvement in ankylosing spondylitis is limited, as is the case in this study. Please note the low median tender and swollen joint counts at baseline. Significant reduction in tender joints was seen with etanercept in the primary study. The same trends were observed in the supportive study. The low baseline swollen joint count precluded our ability to see a significant treatment effect for this parameter.

Acute phase reactants, markers of systemic inflammation, which traditional agents affect only

minimally, responded with significant improvement with etanercept. Represented here is median percent improvement in sedimentation rate and C-reactive protein in both studies. Responses with etanercept are highly significant.

We performed subgroup analyses to verify the consistency of response across treatment subpopulations. Favorable treatment effects were seen in all subpopulations. The panel has been asked to comment on the magnitude of treatment effect in certain subgroups, HLA-B27 negative subjects, women, older subjects, and subjects with a history of psoriasis. As we review these subgroups, we should remember the statistical issue concerning multiple analyses and small sample size.

Responses to etanercept for HLA-B27 positive subjects reflected responses seen for the entire study population. As seen at week 12, a treatment effect was not detected in HLA-B27 negative subjects but was apparent by week 24. The response at week 24 approached significance with a p of 0.06, despite the small sample size.

Addressing the question of gender, depicted here are ASAS 20 responses from men and women at weeks 12 and 24 with significant responses in men and women at 24 weeks.

Addressing the question of age, depicted here is ASAS 20 by age at weeks 12 and 24. In subjects with

ages above and below the median age of 42 years, significant response was seen at all time points.

26 subjects with a history of psoriasis entered the study with 15 randomized to placebo and 11 randomized to etanercept. Depicted here are ASAS 20 responses in subjects with and without a history of psoriasis at weeks 12 and 24. Treatment effect in the small psoriasis population while lower than in patients without psoriasis was present.

The pivotal program enrolled a broad range of subjects with ankylosing spondylitis. Multiple analyses were performed for baseline demographic and disease activity characteristics. Some of the subgroups in these analyses were small. The response to etanercept is extremely robust with demonstration of response in all subgroups, including the small subgroups of HLA-B27 negative and psoriatic patients.

Summarized here are the composite responses at week 12 in the primary study. Proportion of responders with etanercept is consistently and significantly higher for all measures, the ASAS 20, 50 and 70, and DCART 20 and 40, and the low disease state of partial remission.

Summarized here are measures in each of the domains deemed important by the ASAS Working Group. Response with etanercept is again consistently and

significantly higher in all domains by multiple measures. These observations unequivocally establish the efficacy of etanercept.

I will now discuss safety. Subjects were carefully monitored for adverse events. We will first look at all adverse events. I will discuss events which were deemed serious or which led to withdrawal. We'll finally review laboratory abnormalities and antibodies.

Adverse events occurring in more than 10 percent of subjects in any treatment group are depicted here. As expected, injection site reactions occurred more often with etanercept. Injection site reactions were mild and resolved despite continued treatment with etanercept. Upper respiratory infections and injury/accidents occurred more often in etanercept-treated subjects in the primary but not the supportive study.

Here are serious adverse events in the primary study. Serious injuries/accidents occurred in both treatment groups and in the etanercept group were associated with three traumatic bone fractures. Infectious associated with hospitalization were reported in 1 patient in the placebo group and 2 in the etanercept group. 1 subject was hospitalized and withdrew from the study after developing a fever and truncal rash, presumed to be a drug reaction. 1 subject developed lymphadenopathy and was

hospitalized for evaluation. The adenopathy regressed spontaneously and the subject continued on etanercept.

Dr. Burge will discuss serious gastrointestinal events.

The only serious adverse event in the supportive study was a myocardial infarction in an etanercept subject who remained in the study.

This slide presents withdrawals due to adverse events. The majority of these have already been outlined in the prior SAE slide and are shown here in gray. The two additional non-serious gastrointestinal events will be discussed by Dr. Burge.

There were no safety withdrawals in the supportive study.

No laboratory abnormalities of concern were identified in the pivotal program. 2 subjects in the primary study had grade 3 abnormalities in hematology results noted at a single time point, 1 with a low absolute neutrophil count and 1 with a low lymphocyte count. These subjects remained on etanercept and did not report infection associated with these laboratory abnormalities. We observed grade 3 abnormalities in liver function tests at a single time point in 1 subject in the supportive study.

An important consideration with all protein-

based therapies is immunogenicity which can be associated with loss of efficacy and with allergic reactions. To date, this has not been a concern for etanercept. In the AS program, non-neutralizing anti-etanercept antibodies were detected in 3 subjects in the primary study. These antibodies had no clinical sequelae. Anti-etanercept antibodies were not detected in subjects in the supportive study.

We have learned a great deal about etanercept in ankylosing spondylitis. We have clearly demonstrated that etanercept rapidly reduces disease activity by multiple measures, relieves spinal pain and stiffness, improves mobility and subject function, and improves acute phase reactants.

Importantly, ASAS response criteria were achieved at the 20, 50, and 70 percent levels significantly more often in subjects treated with etanercept than with placebo. These differences are highly significant and certainly clinically relevant.

The safety profile of etanercept in patients with AS is favorable.

Dr. Burge will now provide additional perspective and conclude.

DR. BURGE: Thank you, Dr. Tsuji.

As one of the questions set forth by the agency

for discussion today focuses on inflammatory bowel disease, I will share additional observations regarding etanercept therapy in patients with inflammatory bowel disease. I will then represent the AS trials' experience in the context of the broader experience in rheumatic disease with etanercept accrued over the last 10 years. Finally, I will close with an assessment of the benefit-risk of etanercept in the treatment of patients with ankylosing spondylitis.

As previously presented by Dr. Tsuji, 4 patients in the etanercept group discontinued study drug due to gastrointestinal disease events. Reviewing the case detail may provide useful additional perspective.

The first event represented on this slide represents a patient with a history of diverticulitis and multiple previous abdominal surgeries who developed bowel obstruction due to adhesions that resolved after lysis of those adhesions.

The second event is from a patient who developed diarrhea and bloody stools, who underwent complete evaluation by a gastroenterologist, including colonoscopy, which demonstrated the absence of inflammatory bowel disease and the bleeding was attributed to internal hemorrhoids.

The last two events do represent inflammatory bowel disease cases and are included in the following

slide. Approximately 5 percent of patients in each treatment group had pre-existing inflammatory bowel disease, either ulcerative colitis or Crohn's disease. There was 1 patient in the placebo group and 1 patient in the etanercept group that was newly diagnosed with Crohn's disease during the clinical trial. 1 additional patient with a history of recurrent flares of ulcerative colitis requiring systemic corticosteroids discontinued corticosteroids 2 weeks prior to entry into the AS trial and had a flare of bowel disease 1 month into the study.

There were no adverse events attributable to inflammatory bowel disease in the supportive study.

We additionally reviewed the clinical course of patients who entered other rheumatic disease trials with incidental history of inflammatory bowel disease. 14 such subjects were identified. 7 were treated in short-term studies of 4 to 6 months' duration. All completed their study without exacerbation of inflammatory bowel disease. The remaining 7 subjects were included in our long-term clinical trial program. 1 discontinued in the fourth month of therapy due to lack of benefit, and the remaining 6 have been followed on etanercept therapy for a mean of over 4 years and the longest at the end of 5 years. No adverse events related to inflammatory bowel disease have been reported in these patients.

Two randomized placebo-controlled trials have evaluated the effect of etanercept in patients with Crohn's disease. The first trial was a phase II dose-ranging study that included 14 patients treated with placebo and 35 patients treated with etanercept. 50 percent of the placebo group met the pre-defined response criteria compared to 66 percent of the etanercept patients. The proportion of patients that withdrew due to exacerbation of Crohn's disease was greater in the placebo group.

The second study was a randomized placebo-controlled trial performed by Dr. William Sandborn at the Mayo Clinic. He evaluated 43 patients with active Crohn's disease, 23 of these receiving etanercept. As can be seen in this graph, there was no clear impact on the Crohn's disease activity index, the primary outcome measure.

Overall, 80 patients with inflammatory bowel disease have been evaluated in the context of etanercept clinical trials. Data from this etanercept experience, including two randomized placebo-controlled trials in patients with Crohn's disease, do not support an association between etanercept therapy and IBD exacerbation.

As this audience realizes from multiple prior reviews, the etanercept safety profile has been well established. Over 182,000 patients have received marketed

product for over 341,000 patient years. Over the last 10 years, nearly 3,400 patients have received etanercept in prospective clinical trials of rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis. This database includes over 8,000 patient-years of etanercept experience with 1,000 patients into their fifth year of therapy and nearly 400 patients into their sixth year of therapy.

This table demonstrates the rates and events per patient-year of adverse events within etanercept clinical trials in different rheumatic disease populations. Advanced rheumatoid arthritis with or without methotrexate, early rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis is shown on the far right. Whether we evaluate events that are considered serious or non-serious, infectious or non-infectious, the experience with AS is comparable to that observed in other rheumatic diseases.

Etanercept is generally safe and well tolerated in patients with ankylosing spondylitis, and it has generally been accepted that etanercept is safe and well tolerated in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis. The safety experience in the ankylosing spondylitis clinical program has been comparable to that observed in the other rheumatic

disease populations.

In study after study after study, across multiple rheumatic diseases, including late-stage RA, early RA, JRA, and psoriatic arthritis, and now ankylosing spondylitis, etanercept has been associated with unsurpassed efficacy. Etanercept has changed the paradigm for disease management in modern rheumatology care. Across multiple composite clinical response measures, robust efficacy has been demonstrated with etanercept in the treatment of ankylosing spondylitis.

In addition to the robust efficacy observed in the composite measures, consistent efficacy is also demonstrated in each of the domains outlined by the ASAS Working Group cited to be important for evaluating signs and symptoms of ankylosing spondylitis. We've been particularly intrigued by the multiple outcome measures demonstrating improvement in spinal mobility and are hopeful that this finding may translate into improved longer-term outcomes for patients with this often progressively disabling disorder.

As clinicians, a number of us here today have had the experience of caring for people with ankylosing spondylitis. We have personally seen the impact of the disease, the pain, the progressive immobility, and the resultant disability. Both patients and physicians have

been frustrated with the lack of satisfactory therapies for this disorder. In fact, many patients with AS drift away from medical care as they become disillusioned with trials of ineffective therapies.

It is a great pleasure to share with you today data that demonstrates that etanercept provides rapid and dramatic improvements in pain, stiffness, function, and mobility to people who have had no meaningful alternatives. Etanercept with its favorable and well-established safety profile constitutes a much-needed advance for the treatment of patients with ankylosing spondylitis.

If you will recall for many years prior to 1998, there's been no significant new therapies for the treatment of rheumatoid arthritis, and for decades, rheumatologists utilizing inadequate therapies were resigned to accepting a certain degree of persistent disease activity. The introduction of etanercept contributed to a shift in expectation in both the clinicians and in the patients and today, this level of disease activity that was previously accepted is no longer tolerated.

With etanercept, we've been able to improve signs and symptoms, joint damage, improve functional capabilities, and improve quality of life for patients with rheumatoid arthritis. In 2003, we are on the verge of a

similar paradigm shift for the treatment of ankylosing spondylitis. We are excited that etanercept has the potential to improve the lives of so many patients, and I personally feel very privileged to have been able to play a role in the development of this significant advance in the treatment of rheumatic disease.

Thank you.

DR. WILLIAMS: Questions the committee has for the sponsor?

I have one. We're here to discuss the treatment of ankylosing spondylitis, but in your studies, you had several spondyloarthropathies. I believe in 16.0037, there are 15 with psoriasis and seven with inflammatory bowel disease.

If we take out those with other forms of spondyloarthropathies, do we know if there's any change in the safety or efficacy?

DR. BURGE: Yes. We included patients in the study that as long as they met the modified New York criteria, they qualified for the study and that is inclusive of patients who have characteristics of other spondyloarthropathies.

If you'll pull the slide up, please? This slide shows the ASAS 20 response at the primary endpoint of the patients who had no associated diseases on the right

side and those that had ankylosing spondylitis without associated diseases on the left side, and you can see there was robust response in both treatment groups.

DR. WILLIAMS: Was toxicity the same?

DR. BURGE: We saw no differences in the toxicity.

DR. FRIES: I have a string of sort of related questions that maybe you can address. This is a very straightforward and clean presentation of some very interesting data, but I didn't see anything that told me how many centers there were, for example and what the centers were. And I didn't see the consort type of progression in which it's recommended that you identify the pool of potentially available people for a trial, then those people who were screened and considered, then those people who were invited to the trial, and finally those who accepted that. I say that in part because if there's some number of centers and there are 80 patients in a trial, and these centers have as many ankylosing spondylitis patients as I would think, this would represent only a very, very small fraction of patients with ankylosing spondylitis in the target centers.

DR. TSUJI: For 16.0037, the primary study, we had 28 sites in Europe and in North America. There were two Canadian sites. We screened 330 patients and a total

of 284 were randomized and 277 were dosed. In the Wyeth study, 47687, there were 14 European sites, and I'm not certain of their screening numbers.

DR. WILLIAMS: On the ASAS 20, there was an absolute change required. On the ASAS 50 and 70, in addition to 50 percent and 70 percent improvement, was there an absolute requirement for a change?

DR. BURGE: Since there were no published documents of how to perform that, what we did in these analyses is for the 50 and 70 percent response, we required 50 and 70 percent improvement and at least 10 units. There have been other ways that people have calculated that, but this is the way we performed it in this study.

DR. WILLIAMS: Other questions by the committee? Jennifer?

DR. ANDERSON: I have several questions and they just relate to some details, for the most part.

I would have liked to have seen in some of the presentation of mobility results in joints, involvement of joints results, the numbers of patients who had any abnormality at baseline. I know the effects were significant. I think it was on the slides on page 28 and 29. But it would have been informative, I think, to know how many of the patients had the problems at baseline.

And I also would have liked to have seen on

page 33 where you have all the ASAS, ASAS 20, 50, and 70 and so on, one more parameter and that is an ASAS with five out of six that includes the ESR or the CRP and the spinal mobility as components.

And it's also a little bit unsatisfying. I mean, I know everything's wildly significant, but to have an idea of the relative significance of these would be helpful. I mean, this could be done with a test statistic or something.

This is just a methodologist's point of view, but if you can supply these things, I would be very interested to see them.

DR. BURGE: This slide just tells the baseline mean and median scores for the spinal mobility measures. For the occiput-to-wall measure, about 40 percent of the patients had a 0 score at baseline, and so obviously those were normal and were unable to improve. The exact percentage of the patients that have normal Schober's and chest expansion at baseline, I don't readily have.

The second question you asked was about the five out of six parameters. Correct?

DR. ANDERSON: Also about the joints.

DR. BURGE: Oh, excuse me. The joint counts. For swollen joint counts, about 47 percent of the patients on etanercept had 0 swollen joints at baseline compared to

about 53 percent, 55 percent in the placebo group. So roughly half of the patients had no swollen joints, about one-third of the patients had no tender joints.

And the five out of six parameter you asked for -- if you could pull up this slide C-55, please?

The two proposed DCART parameters. I know this might be a little bit of code, but there was two proposed definitions, one of which was a 40 percent response in the ASAS criteria and that's denoted here by the DCART 40. So that's 40 percent in three out of four parameters. The DCART 20 is labeled here. That is 20 percent improvement in five of six parameters which do include the spinal mobility and acute phase reactant.

DR. ANDERSON: Oh, I see. DCART. Okay. Very good. Is that in our package?

DR. BURGE: Yes.

DR. ANDERSON: I see. So DCART 20 does include five out of six. I'm sorry.

DR. WILLIAMS: But the 40 does not.

DR. ANDERSON: But the 40 doesn't, yes. Thank you.

DR. WILLIAMS: Other questions from the committee for the sponsor?

DR. FRIES: Let me follow up my previous question because I was starting to do a little arithmetic

on the back of the envelope here.

So if I understand the centers in the largest study, they contributed an average of about 10 patients from each center. Now, it said that there were 330 invited or screened and 280, whatever the number is, that actually accepted which seems to be on at least in our experience a really huge fraction.

I would suspect that in the centers, there was some kind of pre-screening before you get to the area that you were calling screening; that is, patients that were severely afflicted or patients were advertised for, something so that you actually got 9 out of 10 of them to actually pass the criteria.

We've just run much smaller fractions than that, particularly for a difficult study like this.

DR. BURGE: Clearly, as we were trying to get this study enrolled in a fairly reasonable time frame, each site only was given a significant small sample size at each site. Obviously, these sites had a number of things that they did to try and gather their patient population for this particular study. It had to do with what drugs they were on. Certain drugs were exclusionary. As we said, they could only continue certain disease-modifying therapeutics during that time period, and patients who had complete fusion were excluded.

So overall, we tried to allow a fairly broad range of patients and so the doctors would select from their cohort. I'm sure they had a number of mechanisms by which they did that, by calling patients to see who would be interested in a clinical trial, and some docs by waiting for patients are coming in for their office visits. So there's a variety of ways that different sites may have used to select their patients.

DR. WILLIAMS: Further questions? Jennifer?

DR. ANDERSON: One more about the withdrawals. There were no withdrawals from the shorter study because of adverse events, and I was wondering whether the withdrawals from the primary study occurred in the latter half of that study or not, what the timing of them was.

DR. BURGE: There were 7 withdrawals due to adverse events in the etanercept group in the larger study. 4 of them were within the first half of the study and 3 of them were in the second half. So it was fairly evenly distributed throughout the study.

DR. WILLIAMS: Frank?

DR. VASEY: Could you elaborate on the x-ray changes? I realize it was not primarily a radiographic study. Do you have, for example, any information on the syndesmophytes in these patients? I know if it was a fused spine, the patients were excluded, but say, they had some

cervical range of motion. Were they included in that situation?

DR. BURGE: The only patients that would be excluded are patients who had complete fusion of the spine. There was obviously a broad range of involvement in the spine, and we did collect x-rays in all these patients and we plan to gather further x-rays in the future. But the only patients that would be excluded were the ones that had complete fusion.

DR. VASEY: And how many patients had syndesmophytes? You can still have some spinal mobility and have some syndesmophytes, say, in your lumbar spine.

DR. BURGE: The x-rays have not been formally read at this point.

DR. WILLIAMS: Further questions by the panel?

(No response.)

DR. WILLIAMS: Thank you very much.

We're quite a bit ahead of schedule. However, the FDA needs to break to set up their presentation. So we will take a 15-minute break. I have 13 minutes after 9:00. So we'll reconvene at 28 minutes 9:00.

(Recess.)

DR. WILLIAMS: We will now reconvene.

The next is the FDA presentation which will be made by Dr. William Tauber.

DR. TAUBER: Good morning. Chairman, distinguished members of the advisory panel, ladies and gentlemen, good morning. I have the privilege this morning to present the FDA perspective on the use of etanercept for ankylosing spondylitis.

The FDA perspective has two objectives. One is to confirm the safety and efficacy analysis of the sponsor and the second being to highlight those differences in interpretation of that data that might exist. In general, those areas occur in concert with situations where the data is inconclusive or insufficient and that's why we come to you as the advisory committee to seek your advice and counsel on how to proceed.

Well, the first slide, which is cut off a bit, indicates the members of the team that participated in the review of etanercept. As you can see, perhaps can't see, Chao Wang was our biostatistician and did an excellent job. While we're clearing up the technical difficulties, Chao Wang was our statistician, provided excellent support. Karen Jones was our regulatory project manager and was invaluable. Debra Bower provided our biomedical research, and facility review was done by Daniel Kearns.

So what's being sought here by the sponsor is that Enbrel is indicated for reducing the signs and symptoms of ankylosing spondylitis.

What's the rationale for use of etanercept? Well, you've heard that eloquently presented by the sponsor, but I'll reiterate it very briefly.

Ankylosing spondylitis is a chronic inflammatory rheumatic disease of unknown etiology. Non-steroidal anti-inflammatory drugs have been used and are FDA-approved for use in patients with ankylosing spondylitis. DMARDs, such as used in rheumatoid arthritis, are also used, although are not currently FDA-approved, and importantly neither NSAIDs nor DMARDs have demonstrated the ability to affect the progression of disease in ankylosing spondylitis.

Tumor necrosis factors again have been well presented by the sponsor. They have been determined to be elevated in synovial tissue and in serum of patients with ankylosing spondylitis. That gives you a clue. Etanercept is currently licensed for use in rheumatoid arthritis, juvenile rheumatoid arthritis, and in psoriatic arthritis, and it may very well be that ankylosing spondylitis shares with these other entities similar pathogenic mechanisms.

We're having some technical difficulties again.

(Pause.)

DR. TAUBER: I really wasn't in a hurry to get to the end.

This is slide 6 and on time. I'm going to

explain my methodology, and this is a little bit different than you might have expected. You are certainly accustomed to have your phase II trial procedure, phase III, but I've decided to reverse them. I'm going to talk about the methodology which is very well presented already. I want to talk about the phase III trials because that's where the bulk of the information exists. The phase II trial I bring in as further evidence to support methodology in the use of etanercept for ankylosing spondylitis.

What about the methodology? You've heard the methodology is based on the work of the Assessments in Ankylosing Spondylitis Working Group of which Dr. van der Heijde is a member. So I won't further furnish their credentials which are evident. They created or published in 1999 their evaluation after a number of years of deliberations that determined that there were five domains that were most relevant to the short-term assessment of ankylosing spondylitis clinical benefits. Those were physical function, pain, spinal mobility, spinal stiffness and inflammation, and lastly patient global assessment.

In 2001, they reported, in Anderson 2001, the results of their analysis as you heard earlier of 1,030 patients with ankylosing spondylitis who were treated with non-steroidal anti-inflammatories for less than 6 weeks' time. They analyzed that data and determined that of the

five original domains, four were responsive and you could tell placebo effect from the effect of the non-steroidals. Spinal mobility, it needs to be pointed out, did not show the same responsiveness and was not included in the original ASAS 20 responses.

What about the ASAS 20? You've heard a great deal already but you'll hear some more, and that is, basically for the primary endpoint, just to go over it in some detail, you needed to meet an ASAS 20. You needed to demonstrate an improvement of at least 20 percent or 10 units absolute on the visual analog scale, the VAS, in at least three of the four domains. The patient global assessment, the average total and nocturnal pain, and we've heard the distinction between that and Anderson's work. The Bath Ankylosing Spondylitis Functional Index, the BASFI, total of 10 questions, and the BASDAI or the Bath Ankylosing Spondylitis Disease Activity Index -- glad I don't have to say it again -- the average of the last two questions which conformed to inflammation. And there needed to be an absence of deterioration. So this was the primary endpoint used by both of the studies.

Secondary endpoints were also shared between the two studies, and the color code here is not another glitch in the computer but it's intentional. The white captions indicate those that will be discussed per

protocol, the yellow indicate those that I put at the end of the discussion of the clinical trials, and the green are going to be acknowledged here as being part of the studies but will not be discussed in this presentation.

The phase II and III, back in their proper order, as you've heard, 16.0626 was the randomized, double-blind, single-center, placebo-controlled trial enrolling 40 individuals to receive either etanercept 25 milligrams twice a week or a placebo. The phase III, 16.0037, the larger of the two, which was randomized, double-blind, multicenter enrolling 277, as you heard, at 28 centers internationally, and again etanercept 25 milligrams twice a week versus placebo. And lastly, 47687 which was the randomized, double-blinded, multicenter but entirely European study of etanercept 25 twice a week versus placebo which enrolled 84 patients.

Who were the enrollees? The inclusion criteria, as you've heard, were adult patients 18 to 70 years of age. They had to have a diagnosis of ankylosing spondylitis with a modified New York criteria. They had to have active disease which was defined at baseline as having first a visual analog scale of greater than or equal to 30 for average duration and intensity of morning stiffness, plus you had to have two of the three remaining, either the patient global assessment, nocturnal and total, back pain

and the BASFI 10-question questionnaire.

Those excluded had total ankylosis of the spine, those patients on DMARDs, other than what you see, those that are on prednisone greater than 10 milligrams per day, or those that had non-steroidal anti-inflammatories that were changing.

First study. Design, 277 patients with the active ankylosing spondylitis randomized 1 to 1 etanercept versus placebo for 24 weeks. Randomization was accomplished in the presence of the DMARDs versus no DMARDs. Dosing was the same as you see here.

The primary efficacy analysis was done on a modified intention-to-treat population which was defined as all randomized and receiving at least one dose of study medication. The ASAS 20 at 12 -- and I put in parentheses "and 24" because for the first study, a 24-week endpoint was considered to be a co-primary. If the 12 week was successful, then the 24 could be considered as well. Comparing etanercept with placebo using the Cochrane-Mantel-Haenszel test with stratification again for DMARDs.

Well, who made it? And you've heard earlier about the study completion, but again this is worth shouting about. Randomized and not receiving any medications, there were 284 patients who were randomized, and of those, 3 in the placebo group and 4 in the

etanercept group did not receive study medication. The most common reason, although there were a variety of reasons, for not proceeding was the inability to meet the disease activity criteria.

Those that completed 12 weeks, 96 percent, which is quite excellent, and those that completed 24 weeks was also nearly 90 percent in both the placebo and in the etanercept group.

Discontinuations. Adverse events were an uncommon reason for discontinuation in the placebo group, but as we heard before, 7 individuals in the etanercept group did withdraw from treatment because of safety. As far as what was the most common reason for discontinuation in the placebo group was lack of efficacy, and as you can see, 13 individuals withdrew for lack of efficacy versus 3 in the etanercept group, and there were a variety of other reasons conforming to personal decisions, physician decisions, et cetera, to make up the remainder.

Who were these patients? As you heard, they basically were caucasian men, around 82 kilograms, and HLA-B27 positive and they had had ankylosing spondylitis diagnosed for a mean duration of 10 years.

Baseline characteristics are a little bit sort of squashed here, but the important thing to show is that the four domains of the ASAS were well matched and that

these patients had greater than a median intensity of disease activity at baseline. About 31 percent of patients in both groups had a history of DMARDs and about 14 or so percent of patients had corticosteroids.

One of the interesting things in the analysis, sort of stepping back from this, is that corticosteroids were used in the majority of cases. The three major reasons for which these patients appeared to be on corticosteroids were for uveitis, for asthma, and the most prevalent reason was for ankylosing spondylitis, either through injection or systemic treatment.

Extra-spinal manifestations of inflammatory disease in these patients. Well, as was said before, uveitis is very common in ankylosing spondylitis patients and it was common in this population, coming in around 30 percent. Ocular inflammation likewise also around 30 percent. Conjunctivitis a little bit less. Inflammatory bowel disease somewhere in the 5 percent and psoriasis somewhere around 10 percent, well matched between the two study groups.

So where did this take us? This is the primary endpoint, and as you can see and have already seen, the ASAS 20 at 12 weeks, there was a 33-point treatment difference between etanercept and placebo. At 24 weeks, that treatment delta had increased actually to 35, and both

of these values were statistically significant.

You've heard about the ASAS 50 and 70. I want to spend just a moment talking about how they were calculated. I think you have heard this but it bears repeating, and that is, that ASAS 50 represents a 50 percent improvement but does not represent a change in the absolute numeric increase in points, only 10. It's the same as ASAS 20 and the same is true for the ASAS 70, that 10 points, but you do need to have greater levels of improvement subjectively. 70 is just the next order up.

Graphically -- and I was reflecting earlier that I seem to be inverted, whereas I presented etanercept as blue, it was presented as yellow just previously. I'm not sure of the significance of that, but in any event, the 20/50/70 of both 24 and 12 weeks are presented here. The thing to point out is that etanercept has a greater effect than placebo in each one of these. At 70, you have 29 percent of patients at 12 weeks on etanercept reach the ASAS 70 compared to only 7 percent of those patients that received placebo. At 24 weeks, those numbers are very similar with 28 percent of the etanercept patients reaching the ASAS 70 compared to only 4 percent of the placebo patients. All these values were statistically significant.

Partial remission has been introduced as a concept. The actual definition. It was proposed by the

ASAS Working Group. Actually, it appears, to my vision, in the presentation in 2001, the Anderson study, and it was part of the original deliberations on the five non-steroidal anti-inflammatory studies. It was felt that it would complement the response criteria, that it would allow for cross-trial comparisons since it obviously, if you had patients -- that enrolled mostly severe patients, they may not improve to this level and those that have mild disease might not be able to improve as much.

The way it is defined is a less than 20 on the visual analog scale in each of the four ASAS response criteria and you see them listed here.

Graphically, at week 12 and week 24, there is a higher response in the etanercept recipients than in the placebo for this particular parameter. These are nominally statistically significant.

The next secondary endpoint was the individual components of the ASAS Working Group response criteria, and as has been shown -- this is only one study at a time -- in every instance, there was no one parameter that seemed to be out of balance or in a different direction than the others. They all showed the etanercept to be superior to the placebo and that each one individually achieved at 12 weeks statistical significance.

Acute phase reactants, sedimentation rate and

C-reactive protein. There are a couple of things that I want to illustrate from this slide, the first of which being that although the numbers are elevated, they're only slightly so. These are the medians, and I've included the medians because in the placebo group for sedimentation rate, that's actually within the normal range. It's only mildly elevated in the etanercept group. C-reactive protein, the medians are actually within the normal range. This is not a disease that manifests itself with a great deal of acute phase reactant positivity high numbers. That being said, etanercept still was able to improve the level of the sedimentation rate and C-reactive protein and achieved a p value of less than .001.

The DCART 20 and the DCART 40. This was presented as an exploratory analysis, and I'll handle it as such. The DCART 20 again uses the four criteria of the ASAS response criteria that we've mentioned, plus it adds chest expansion for spinal mobility and C-reactive protein for acute phase reactants. DCART 20 has the same requirements for the first four and the other two have to have a 20 percent improvement relative to baseline without an absolute numeric change. A DCART 20 requires five of six to demonstrate 20 percent improvement without worsening the remaining domain.

One of the things I would like to point out is

that it is very easy to see that you could achieve five of six positive and leave spinal mobility out. It could be that spinal mobility, which is the fifth domain, is not seen by the DCART 20. The DCART 40 is not the next big brother of DCART 20. DCART 40 is actually a different system which uses the ASAS Working Group criteria, holds them to a 40 percent response and requires a 20 unit improvement rather than a 10 without worsening in the remaining domain.

What does it look like? You've seen this earlier. In using the DCART 20 and the DCART 40, etanercept did achieve higher values of DCART 20 and DCART 40, and these values actually are somewhat similar to the ASAS 50, as would probably be anticipated since they share similar methodology, and they did achieve a p value that was statistically significant.

What follows is a number of exploratory analyses. The first of these is did having a non-skeletal inflammatory condition make a difference? Did those patients who have them fare differently when they received etanercept? What we found is that having uveitis, having inflammatory bowel disease, having any of these risk factors for reactive arthritis did not appear to confer any disadvantage to the etanercept recipients. There seemed to be no discernible difference between etanercept recipients

who had these conditions and those who did not.

That being said, psoriasis -- and you've seen this earlier and probably the mirror image color-wise which demonstrates that at 12 weeks at least, that patients with psoriasis, of which there were only 26 -- and we have to interpret this data with caution because of the small numbers involved -- achieved an ASAS 20 of 45 percent compared to 61 percent in those who did not have a history of psoriasis. Again, this is a very small group and we bring it up for your deliberation.

What about other baseline variables? Well, other things that have made differences in other studies were all certainly looked for here, race, weight, disease duration, and geographic site, and none of these demonstrated a significant impact on the treatment effect with etanercept. We were particularly astonished to see the lack of effect of disease duration, that actually those patients that had ankylosing spondylitis diagnosed longer appeared to have a very similar response to etanercept.

But age -- and you've seen this earlier but you're going to see it a little bit different in presentation, and what I have here is all of the age groups broken into quartiles. And I guess I'm distressed to see the 50 and older are the last quartile but I guess that's that. What you see is a stair step approach or stair step

of decreased efficacy with each quartile. So that, each generation seems to get a different effect with etanercept. The placebo seemed to remain relatively constant, but again there seems to be a relentless decline.

What about gender? And this again was presented. There were 67 women that were participants in this study. Of those 67 women, at 12 weeks, ASAS 20, they reached ASAS 20, about 45 percent, compared to about 65 percent in their male counterparts.

What about baseline disease severity? It certainly would make sense that if those are more severely affected would have perhaps, say, lesser response or perhaps even a greater response. Actually, on analysis, we found that those patients that were above and below the median for all four of the domains had very comparable responses to etanercept. They did not seem to be at a disadvantage to having more disease severity. The same thing is true with the presence or absence of hip disease which is considered to be a poor prognostic factor, and this did not seem to impact the responsiveness to etanercept.

What about concomitant medications? Well, the effect size for etanercept at 12 weeks did not seem to be affected by concomitant use of non-steroidals of which it seemed like everyone -- about 90 percent. Corticosteroids,

there were 36 individuals who were on them, and there did not seem to be an impact. DMARDs, 87 in total, and of those breaking it down to two, the two most prevalent of the DMARDs that were permitted in this study, sulfasalazine and methotrexate, again, there did not seem to be a significant impact on etanercept whether or not you were on these medications or not.

Again, this is the last of the exploratory analyses that I'll present on this study, and this is the ASAS 20 at 12 and 24 weeks for HLA-B27 positive versus negative. You'll notice that there were 217 patients who had an HLA-B27 antigen test done and were found to be positive. There were 40 patients -- I noticed you had 41 -- that had HLA-B27 tested and found to be negative. So again, the numbers are small.

At 12 weeks, the HLA-B27 negative population, there is an improvement compared to placebo, but it does not achieve statistical significance, and it is lower than the HLA-B27 positive. At 24 weeks, there is some improvement and some narrowing of the gap between the two, but again the HLA-B27 negative population has a lower response compared to their HLA-B27 antigen positive counterparts.

Moving on to safety, I've highlighted in yellow those factors. This is greater than 5 percent as opposed

to a little bit longer list than was presented. Highlighted in yellow are those categories where there is a numeric imbalance between the two arms. And again, infections, injection site reactions, and accidental injury appear to be the most important of these adverse events. We speculated on the possibilities for the accidental injury, whether patients felt so exuberant that they were going skiing, but it turned out most of these were motor vehicle accidents and occupational hazards.

Important safety outcomes. Serious adverse events, as you've heard, there were 9, or 7 percent, in the etanercept group versus 5 in the placebo group. Withdrawals for safety which we'll touch on in a minute, 7 versus 1, 5 percent versus 1 percent. Grade 3 and 4 adverse events or infections, 14 versus 4, and abnormal laboratories, you've heard already, there were two instances of hematologic laboratory abnormalities that were grade 3, an ANC that was low and a lymphocyte count that was low. Both of these resolved without intervention.

Percent serious adverse events. The totals, 4 percent and 7 percent. The accidents, there's a 1 percent increase and a 1 percent increase for gastrointestinal, but infections and fevers seemed to be, comparing the two arms, the more prevalent of the serious adverse events driving the differences between the two arms.

Withdrawals for safety. There were, as you have seen, 7 withdrawals in the etanercept group versus 1 in the placebo group, a patient who made a suicidal attempt and was the only grade 4 adverse event in the study. Accidents, there were 2 among the 4 that prompted withdrawal in the etanercept group. Infections/fever, 1. Gastrointestinal, we'll speak on a little bit more, but it's already been treated on, and psychiatric was the 1 patient with the suicide attempt.

Infections of all intensity. There were 2 serious infections, grade 3 infections. Both of them were cellulitis. Both of them were due to animal bite and both required IV hospitalization and IV antibiotics, and there was one viral infection on the placebo side that received IV antibiotics pending evaluation. Most of the remainder of the infections, however, were of mild or moderate intensity. If you take out upper respiratory tract infection, the larger numbers of etanercept patients with infections really becomes fairly comparable between the two arms. So upper respiratory tract infections appear to be more prevalent in etanercept patients as has been seen in other studies.

Summary of efficacy for this study. The etanercept 25 milligrams twice a week was superior to placebo in achievement of ASAS 20 response criteria at both

12 and 24 weeks. The treatment difference is 33 percent. DMARDs did not appear to affect the difference. Prognostic factors potentially associated with lower response: older age, female gender, HLA-B27 antigen negativity, and concomitant psoriasis.

Our summary of safety for this study. Etanercept 25 milligrams twice a week had a higher observed incidence of certain adverse events compared to placebo. There were more serious adverse events. There were more withdrawals for safety. There were more grade 3/4 events and infections, and of the 7 safety withdrawals, there were 4, as you've heard. Of the 2 patients that were diagnosed with inflammatory bowel disease, 1 had a prior history of inflammatory bowel disease and 1 was a newly-diagnosed patient with inflammatory bowel disease.

Moving to the second study, in this, we start to pick up the speed here because the predominant amount of information is contained in the first study.

The protocol enrolled 84 patients again with active ankylosing spondylitis, again randomized 1 to 1. The treatment duration was 12 weeks versus 24. Randomization was also done with DMARDs involved. Dosing was etanercept 25 milligrams twice a week or placebo, and the primary efficacy analysis once again is the modified intention-to-treat population, all randomized to one dose

of medication given, and the ASAS 20 at 12 weeks compared etanercept to placebo using the Cochrane-Mantel-Haenszel test with stratification for DMARDs.

What about the populations? As you've heard, one of the things that doesn't appear here, there was a slightly longer duration of disease in the etanercept patients in this study of 15 years, a mean duration then in the previous study, but otherwise the durations were the same, around 10 years.

There were some other exceptions. There was a lower mean weight, 75 kilograms versus 82 kilograms. There was a prior use of DMARDs. This is prior use, not necessarily concomitant use, was higher in the study 2 population at 69 percent, and this might reflect the 15 years of duration. And there was a lower incidence of ocular inflammation, 16 percent versus 30 percent, uveitis 22 percent versus 30 percent. There was a bit higher psoriasis, 15 percent versus 10 percent, in study 1, and the incidence of inflammatory bowel disease again was around 5 percent.

I cheated a bit on this slide because I've included two things. I have the completed 12 weeks along with the primary endpoint, and this is again to highlight the fact that there was very good participation for 12 weeks in the study. 100 percent of placebo completed 12

weeks, 96 percent of etanercept patients, and neither of the etanercept patients withdrew. The 2 that withdrew withdrew for adverse events.

What was the value? What was the answer? What is found is an ASAS 20 at 12 weeks for etanercept of 60 percent versus 23 percent which is a statistically significant difference.

Using the ASAS-defined partial remission -- this is unfortunately a little distorted. One of the things that we would point out here is that there is greater response, there are greater numbers of etanercept patients who achieve the ASAS-defined partial remission but that it does not, in this study at least, reach statistical significance.

Looking at adverse events of all intensities, again the code here is if it's yellow, there's a bit of an imbalance, and as you can see, injection site reactions, injection site ecchymosis, and asthenia were more prevalent in etanercept. Infections seemed to be fairly well balanced in this particular study. Perhaps upper respiratory tract infections weren't an issue.

Important safety outcomes. One of the things that you first see when you look at this study is that there's very little on there. There was one serious adverse event in one gentleman who had a myocardial

infarction and he also contributed to the grade 3/4 abnormal laboratory through elevated liver function tests.

In terms of withdrawals for safety, there weren't any. In terms of grade 3 and 4 adverse events, there are 4 versus 2, which seems like a fairly similar number to me.

Looking at the last study -- and again this is going in sort of a backward way -- this study enrolled 40 patients with active AS, again randomized 1 to 1 to etanercept or placebo for 16 weeks. The dosing was etanercept 25 milligrams twice a week versus placebo. Modified intention-to-treat population was again used, all randomized and receiving at least one dose of study medication.

This, because this did antedate the development of ASAS 20, had pre-specified ankylosing spondylitis criteria which needed to gone over a bit in detail. 20 percent response at 16 weeks in three of five pre-specified ankylosing spondylitis criteria with one of the improved measures being spinal pain or morning stiffness without worsening in the remaining two.

For patients without joint swelling, one of the five measured elements -- and as we heard earlier, about 50 percent of patients, at least in the first study, had no joint swelling at baseline -- then improvement was required

in three of the four remaining elements without concurrent worsening in the remaining one.

These are the five in some detail because again not only are they very much more to talk about. Patient global assessment was done using a five-point scale over the past week. Improvement was designated as a decrease of one.

Nocturnal spine pain used the visual analog scale of 100 with an improvement of 20 percent in millimeters.

Duration of morning stiffness was determined in terms of minutes in the day preceding the clinic visit with 20 percent indicating achievement of the criteria.

The last two, the BASFI 10 questions, and the swollen joint score, peripheral joint swelling at 44 diarthroidial joints rated on a 4-point scale, 0 for no swelling, 1 for mild, 2 for moderate, and 3 for severe. Improvement defined as a decrease in joint swelling by 20 percent in swelling score. If the swollen joint score was 0 at baseline, clearly you had nowhere to go but down.

What was the result using this particular criteria system? I've included week 12, although it was not one of the primary endpoints. I do this to compare it with the studies we discussed so far which did use the 12 weeks. At 16 weeks, using the pre-specified criteria just

described, 75 percent of etanercept patients achieved a 20 percent value on the pre-specified criteria versus 25 with placebo which was statistically significant. It was also statistically significant at week 12, and this is down in the 45 percent treatment difference between etanercept and placebo at week 12 using the pre-specified.

Well, an ad hoc analysis was done. The ASAS Working Group published their criteria, and this study was looked at with a modified ASAS 20 criteria. The reason I say modified is because obviously the data was collected in a different way and needed to be converted. The conversion was done by converting the global assessment to a visual analog scale, and the morning stiffness had to also be converted to a visual analog scale from number of minutes with greater than a 120 minutes being rated as 100, and then five-sixths of whatever the number of minutes became the visual analog scale.

At week 12, again which would be comparable to the two previous studies, you see that 65 percent of the etanercept patients have achieved this modified ASAS 20 versus 25 percent of the placebo, and at week 16, which was the endpoint, it's 85 percent versus 25, both of these values being statistically significant.

This study included a few other analyses, one being the total back pain. This is the Dougados

Spondylosis Functional Index and lastly the Krupp's Fatigue Measurement. I include them here because again they add more to our understanding of the methodology of looking at ankylosing spondylitis. In each of these, etanercept did demonstrate greater efficacy than did placebo and these all were found to be nominally statistically significant.

As promised, spinal mobility. Though we've gone back to study 1 now, we're going to look at spinal mobility, and what I have graphically presented here is at 12 weeks, what is the spinal mobility determination in the first study. As you can see, the Schober's test shows the least increase. Chest expansion and occiput-to-wall all achieve a nominal p value of less than 0.05. So it is possible to see improvement in spinal mobility with etanercept.

Using the study 2, again the three parameters that were evaluated, the Schober's test does achieve a nominal p value at 12 weeks of less than 0.05, and the other two demonstrate higher activity in the etanercept group, but these do not at 12 weeks achieve statistical significance.

Lastly study 3, none of these -- they all show improvement but none -- again, the same recurring theme that they did show improvement in the spinal mobility. They did not at 12 weeks achieve even a nominal p value of

statistical significance, but what isn't show here is that at week 16, that occiput-to-wall and Schober's test did achieve statistical significance, and the remaining parameter was very close at 0.05.

Swollen and tender joints. This is again from study 1. The point to be made -- and I think it's already been well discussed -- is that tender joints did demonstrate a statistical nominal p value of less than .05 in study 1 at 12 weeks, where swollen joints did not. I guess one of the things that sort of struck me was that there were a number of patients that, when your placebo is performing at that level, it's very hard to achieve that, but the tender joints certainly did demonstrate statistical significance.

This is the final conclusions on efficacy. Etanercept was demonstrated to be statistically superior to placebo in three trials assessing symptomatic treatment in active ankylosing spondylitis. Older age and female gender were associated with lower response rates. I can say that up a little higher because the numbers were greater, but then I'll lower my voice and say that in HLA-B27 negative and that in psoriasis, I also saw some decreased performance, and I don't know the significance of that.

Methodology. The results used in the ASAS 20 generally demonstrate responses of similar direction and

magnitude to previously-used measures used in the assessment of therapeutic benefit in ankylosing spondylitis. By that, I mean the Dougados Spondylosis Functional Index, the Krupp's Fatigue Measurement, et cetera.

In terms of safety, our conclusions are that the safety profile of etanercept in ankylosing spondylitis is similar to that seen in rheumatoid arthritis and other indications. That being said, there were more withdrawals for inflammatory bowel disease in etanercept patients compared to placebo recipients in study 1 but the numbers were quite small.

That concludes my talk. Thank you very much.

DR. WILLIAMS: Does the committee have any questions for Dr. Tauber of the FDA?

DR. ANDERSON: I'd like to make a comment about this modified ASAS 20 and the use of the term "converting to VAS" because I think that's a bit misleading because a VAS was not actually completed by anybody, but I think it would be more appropriate to say that the measure was converted to a 0 to 100 scale rather than a VAS.

I think that spinal mobility results would be more informative if you had the n's involved in each case. Neither this presentation nor the FDA's presentation actually shows sample sizes.

I guess this is just for future reference for thinking about what kinds of measures are useful and how consistently useful they are and what proportion of the subjects they're relevant for. That's all. I don't know whether either FDA or the sponsor would want to respond to either of those right now.

DR. WEISS: Thank you for your comments on the issue of the conversion. I think that's a very good comment.

I agree it's not shown on the slide, but in the briefing document, the tables, for instance, looking at page 20, table 13, "Endpoints of Spinal Mobility Parameters," and we do have the total n's for this study.

I guess the question I would actually ask our reviewers. I'm making the assumption that everybody in the trial or nearly everybody in the studies actually had spinal mobility testing done. We don't have any information on if there's missing values and imputation, but we have the total n's which is actually the sample size for the trial.

DR. SIEGEL: I think the total number of patients who had spinal mobility measured was the whole population. I think what Dr. Anderson is wondering about is how many of those patients had an abnormal spinal mobility to begin with, so where improvement would be

relevant. Is that what you were --

DR. ANDERSON: Yes.

DR. SIEGEL: And we don't have that information.

DR. BURGE: Yes, we do. I shared with you earlier the number of patients that had 0 scores in the occiput-to-wall score. What we used is a cut of 5 centimeters being a surrogate for normal for the Schober's and for the chest expansion, and at baseline, about 10 percent of the patients had a normal Schober's test and 12 percent in the placebo and 17 percent in the etanercept group had a normal in the chest expansion measure.

DR. ANDERSON: What was the percentage? It was like 40 percent?

DR. BURGE: 40 percent for the occiput-to-wall.

DR. ANDERSON: Thank you.

DR. WILLIAMS: Jim?

DR. FRIES: It's a very interesting set of studies because the results in this population are so dramatic. I would guess that it wasn't really at the end of the study a double-blind study for either the examining person or the patients. I don't say that as anything against the results of the study but do suggest to the FDA that what we recommended on other occasions is that at the end of a study, one debriefs the investigator and the

patient with regard to which arm of the study they guessed they were on before they're actually informed.

In this instance, I guess if people threw away their bed and got up and walked, that they'd have some hint after 10 years of disease that they were on something that they hadn't been on before. It's an interesting thing because in some ways, it represents for subjective values a source of potential bias. It's also, viewed from another way, a real statement of effectiveness, if in fact it was making a change.

DR. WILLIAMS: Dr. Walton?

DR. WALTON: May I ask from the aspect of unblinding, whether you're thinking that the unblinding is more from effectiveness or whether the side effects, for instance, from the small injection site reactions contributing an unblinding effect, whether you think of that?

DR. FRIES: This is pure speculation, and I don't even know if it should go on the record. Numerically, I think it was probably the effectiveness, but many patients must have also had some injection site reactions. So it would be sort of confirmatory in that. It's just that they did have some clues.

I've had this feeling that essentially all randomized, controlled trials suffer to some degree or not

from lack of blinding, and we've made a habit of doing these debriefings at the end, and they always are significantly greater than 50/50 with regard to the patient and the investigator identifying the active arm of the trial. So it's an interesting thing because we say double-blind and we go through all of these protocol things, but in fact there are little clues.

In a lupus cytoxan study some years ago, they gave everybody wigs because they anticipated that the alopecia would be that, but the patients still knew despite the wigs. Just a side point really.

DR. WILLIAMS: I think it's fair to say that there's a potential for unblinding. It really was a blinded study in the traditional sense of the word.

Did you have a comment?

DR. BURGE: I would just like to share some data about you particularly mentioned the injection site reactions. If you can show this slide? Because we did look to see whether the injection site reactions would have had an effect on the responsiveness in this study. As you can see, you can see the results in both studies of those patients with and without injection site reactions and really the response rates between those with injection site reactions and those without were very comparable.

Additionally, the assessors from the sites were

all blinded to all the other aspects of disease and so the global assessment done by the assessor was not involved in patient care or in any other way involved with the patients to try and maintain this kind of blinding.

DR. WILLIAMS: Other questions or comments?

DR. WALTON: Could I make a comment on the unblinding issue?

DR. WILLIAMS: Jeff?

DR. WALTON: Dr. Fries, I think that we've thought a lot about these concerns about potential unblinding that you can run into, especially with studies of agents with large effect sizes where the investigators and patients can both be unblinded. We've approached it in a number of different ways.

One is to include independent blinded assessors, where possible, although since so many of the outcome measures here are from the patient, there's no way to unblind that.

Other things that we've done is to look at the patients who don't have unblinding side effects, as you just saw with the injection site reactions.

Another approach is to use two different doses of the product. With the original etanercept study in rheumatoid arthritis, 10 milligrams and 25 milligrams were both investigated, and they had similar unblinding side

effects, and the effect size was different between the two, but this is always a problem.

We have thought about using assessments of the investigator and the patient about what treatment arm they thought they were on, but it's not clear exactly how you would use those answers. If you could explain all of the efficacy in terms of unblinding, would that necessarily mean that the result was invalid? It's a little bit difficult to know how to use that.

DR. FRIES: Yes, I agree, and I agree with Jim, that by any of the usual standards, this was a randomized double-blind trial, and I didn't really mean that to be taken as a serious criticism. I just do find it a very interesting area and those of us who like measurement and who have done a lot of these measurements in people know that if you're getting improvement, let's say, in a Schober, that could be a decrease in inflammatory activity. It could be a decrease in pain activity, allowing different kinds of effort levels because there are effort levels. So I just find this an interesting area to kind of try and analyze just a little bit.

DR. WILLIAMS: If a trial has the potential to be unblinded, it's either a very effective or a very dangerous drug.

Gary?

DR. HOFFMAN: Dr. Tauber reviewed with us the differences in quartiles regarding age and pointed out the decreasing efficacy with each increasing quartile, and I was wondering, it may be in the briefing book but I didn't recall the data, how many people were in each of those quartiles and how robust was that data as we got up into the quartile that was over 50 years of age? So the crux of that question is, is this really robust? Is it quite convincing that we lose efficacy with age?

The other question tied to that perhaps that the sponsors could address as well is, as with conventional agents, as the biologics are being developed, do we have the means by which we can evaluate differences in metabolism with age, clearance? We're aware of immunologic senescence with age. Are these factors that are playing an important role in response to therapy? So perhaps first Dr. Tauber.

DR. WILLIAMS: Dr. Tauber?

DR. TAUBER: My understanding is that the quartiles in etanercept are approximately 40 individuals per quartile and that -- no, I'm sorry. It would be somewhere in the neighborhood of 30 individuals per quartile because there were a 140 individuals totally who received etanercept. These were, as I understand it, equally divided. So I would have no anticipation that one

group was given a larger number than the other.

DR. WILLIAMS: Dr. Burge?

DR. BURGE: Yes. We've put the slide up here for you, Dr. Hoffman, to show the different breakdowns of the quartiles that are represented, and as Dr. Tauber said, it's roughly, when you do it by quartiles, we have a quarter of the patients. There's a little bit of unevenness in the two treatment groups as you make fine cuts. You can note here that we put both the 12- and the 24-week data on these different breakdowns, and we have statistical significance at the .05 level at all those, except for the older patients at the 12-week time point.

DR. HOFFMAN: Do you also have any data that you might be able to share with us regarding metabolism clearance?

DR. BURGE: We don't have any data on that.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I can perhaps make one additional comment about --

DR. BURGE: I do have one comment I could make to that. Excuse me, Jeff. We've not seen differences in serum concentrations, et cetera, from patients with different age groups, but that's really the limit of what we have on serum concentrations.

DR. SIEGEL: In terms of your question about

the robustness of the finding, we didn't perform statistical tests to see whether there was a statistically significant association between age and response rate.

When we do these analyses, we consider them exploratory. They're intended to see if there are any patient group who doesn't have the benefits seen in the study population as a whole, but they are by their nature exploratory.

DR. WILLIAMS: Other questions for the FDA?

(No response.)

DR. WILLIAMS: Then that will conclude this portion of the session.

We are an hour ahead of schedule. We will have the open hearing at 11:30. I think we'll begin to discuss the questions but we won't take any votes until after we've had the open hearing.

So if the committee could turn to the questions. I will not read the preambles to each one. You have them in front of you. Question number I has two parts. Do the results from these clinical trials demonstrate that etanercept is effective in patients with ankylosing spondylitis, and (B) if licensed, do the data support an indication of reducing signs and symptoms? After the open hearing, we will vote on this question, but we'll discuss it at this point.

Any comments? Jim?

DR. FRIES: This is in a sense the crux of the issue, and I wanted to ask the sponsor and other people perhaps if they had -- I'm sure that the sponsor's people have read the Canadian Rheumatology Association paper which came out last month on this same subject that we're dealing with here now. And I wondered if there were comments on appropriateness or inappropriateness of the conclusions of that paper from the consortium group in Canada.

DR. WILLIAMS: Dr. Burge?

DR. BURGE: Clearly the reference there is that they recommended in that consortium the use of NSAIDs first in the treatment of ankylosing spondylitis and that since there's no other therapies that have been effective for spinal disease, that following ineffective therapy or inadequate therapy for non-steroidals, that TNF inhibitors are appropriate for that. They're the only therapies that have been shown to be effective, and I don't think we have any issues with that recommendation at all.

DR. FRIES: Let me see if I can make an issue. What they basically came down to is what you said, although they also included infliximab in their analyses. Infliximab and etanercept are indicated for reduction of signs and symptoms of moderate to severely active spondyloarthropathy in patients who have had an inadequate

response to maximum doses of two non-steroidal anti-inflammatory drugs over a 3-month period of observation and either sulfasalazine or methotrexate is indicated in those with predominantly active peripheral arthritis. So in fact, to me, this is sort of what we heard here today.

But the issue with regard to the question that's before us here, like do they demonstrate that etanercept is effective in patients with ankylosing spondylitis, and presumably in the context of this discussion, that means these 350 putative patients out there. But the patients that have been studied are patients with moderately to severely active ankylosing spondylitis selected clearly from the universe of all patients.

So that, if I was asked the question of has it been shown that these drugs are effective in ankylosing spondylitis unqualified, I think the answer to that probably would be no. It's been shown rather dramatically that in selected patients with ankylosing spondylitis, it is extremely effective and well within a safety range.

DR. WILLIAMS: I would be satisfied if you just said active ankylosing spondylitis because they didn't really classify them as moderate or severe but only as active as defined, and so I agree that of the 350,000 patients or however many you want to quantify, that there's

a certain percentage of those that don't have much in the way of signs or symptoms. But the patients studied were considered active, not necessarily severe, and I'd put active in front of ankylosing spondylitis.

Other comments? Frank?

DR. VASEY: At some point, I wanted to raise the issue about the radiographic picture in assessing whether this is a disease-modifying approach or whether we're just treating symptoms. I think the ideal way to look at that would probably be via x-ray. So I'd be interested in comments from others how we might proceed along those lines.

DR. WILLIAMS: You're welcome to comment on it now. We're talking about efficacy, and I can't see that we discuss that question later on.

DR. FRIES: It was interesting in the development of the various criteria for improvement that radiographic -- well, even spinal mobility on the basis of the NSAIDs studies wasn't considered an endpoint because it hadn't moved much in those studies, and it obviously should be a part of things in the future as we move to more powerful drugs because it does look like it's something that you can change and that's probably something better than the signs and symptoms. It's something to do with spinal mobility.

The next extension of that would be the probable definition of disease modification which would probably be radiologic, and if that were done and obviously it shouldn't be done at this point, I mean, if one was to get into that interesting question about what would happen with these new agents over a 5-year period with radiographic endpoints, I think it'd be exceedingly interesting. And at some later point, one could consider the question of whether it was possible to achieve disease modification in appropriately selected patients here.

DR. WILLIAMS: I'd like to ask Frank a question since you're our resident expert. How impressed are you with the changes in the clinical signs of mobility?

DR. VASEY: Well, I think those clinical signs raise an interesting question. I mean, obviously they're useful and important, but do they reflect sort of resolution of muscle spasm, for example, or are they really affecting the x-rays? I think it's sort of an unanswered question. So personally, I agree with Jim. I think the radiographic improvement would be the ideal way to approach the issue of disease modification. And I think we really need to know this.

I think the company has fairly presented some of the risks of the drug. Obviously, practicing physicians are weighing the risks versus the benefits. There's some

risks we haven't talked about which I think are beyond what we're doing at this panel, but I think certainly we need to know the benefits and it'd be very nice to know whether we're just treating symptoms or whether we're actually modifying the natural history of the disease and preventing spinal fusion radiographically.

DR. WILLIAMS: Wendy, do you have any comments on these first two questions? The first question with two parts.

MS. McBRAIR: I'm just excited to see such positive results for patients with ankylosing spondylitis because clearly there has been a dearth of helpful medications for these folks, and I would like to see continued studies on the actual effects and effectiveness. Obviously that's important. This is a great first step.

DR. WILLIAMS: Gary?

DR. HOFFMAN: I'll just toss out a comment to bait some of our colleagues around the table and our colleagues at the FDA. I have difficulty with the concept of disease modification always being referred to as ultimately affecting x-ray progression. If a drug modifies pain perception, mobility, quality of life, activities of daily living, I think that reflects profound disease-modifying activity on the part of a drug and measuring radiographic parameters, I think, is also terribly

important but shouldn't be the sine qua non for disease modification. I would appreciate people responding to that.

DR. FRIES: I totally agree. I've been for functional and quality of life end measures as well, and I agree with your point. It's been the experience in rheumatoid arthritis, though, that there are some members of the mass of people who look at data that are fixated on the radiographic change to a greater extent than you and I are, and so there's a certain amount of credibility, I think, that comes when you have slowed the rate of erosions or, in this case, slowed the rate of bony fusion, if that was achieved.

So I would certainly do area under the curve quality of life, HAQ disability measures, look at work disability and frequencies of leaving the work force and a whole variety of other measures as well. I think we're all impressed that these are shortish studies. These are not real long-term studies when you have a disease for 40 years and we're going to study it for half a year. So it's clear that there are longer-range questions and the disease modification issues need to have a sufficient scope of time so that you can say that the predicted course has actually been changed, the trajectory has been changed.

DR. WILLIAMS: I actually agree with Jim, but I

would put a different interpretation on it. I think disease modification has many different definitions and one is that you relieve pain and that modifies the disease.

However, if we use rheumatoid arthritis as the example, we know that we have relieved the signs and symptoms with continued deformity of the disease. So that, in that case, we did refer to stopping the progression of the disease and the destruction of the disease which was best measured by radiography.

Now, in that sense, I would think that the same would be true with ankylosing spondylitis, that if you want to say you've stopped all aspects of progression, you have to include radiographic, whether that's plain radiographs or MRI or whatever, but to show that you have no longer got destruction going on, even though you've modified the signs and symptoms. But I would also agree that there are a lot of different definitions to disease modification.

DR. HOFFMAN: Along other lines, I think we've all enjoyed seeing the impressive results from these three trials. On the other hand, one might ask for the patients who were partial responders, as was most everybody who responded, whether there is ongoing experience with higher doses for people who have not had satisfactory responses. Perhaps our colleagues or our sponsors might respond.

DR. WILLIAMS: Dr. Burge, do you know, has

there been any experience with higher doses of etanercept in those who did not respond to the standard dose?

DR. BURGE: There's no experience in ankylosing spondylitis of looking at higher dose. So we don't have data in ankylosing spondylitis. We have looked at it in rheumatoid arthritis in a small study and have looked at it in other diseases as well.

DR. WILLIAMS: Mike, we haven't heard from you. Anything you have to say about this first question?

DR. FINLEY: Well, I concur with Jim's and Gary's points about the notion of disease modification encompassing -- I'm certainly an advocate, thinking about patients, for quality of life and work place disability. And I'm not sure we know, with regard to AS, the natural history in the setting of biologics like etanercept. We have a better sense of it because of our experience with RA and that association with x-ray change, but we're all aware that in patients with AS, there's variability in their x-ray change and how that -- the ones that are very severe and are fused, they clearly have disability. But there are then gradations of those who have various parts of the spine who are involved that may be more disabled than others, and I think as we go forward longitudinally, that would be the thing that I'm most interested in, particularly with regard to disability.

DR. WILLIAMS: Jennifer?

DR. ANDERSON: I'd like to compliment the sponsors on doing studies with very low dropout rates, and I think it shows, even though these are relatively short studies but even at 24 weeks, the dropout rates weren't so very high. With dropout rates this low, almost how you handle the data for the dropouts isn't going to have a dramatic effect on the results and their interpretation.

However, I would be interested to know, because I haven't been able to find it, at least in the material today, just how dropouts were handled. Was their last observation carried forward or was information gathered on patients even after they had dropped out and used in defining the final outcomes?

DR. WILLIAMS: Dr. Burge?

DR. BURGE: The primary outcome variables are dichotomous, and for those dichotomous variables, when people discontinued study, we considered them non-responders for the dichotomous endpoints. For continuous endpoints, we used last observation carried forward after they discontinued.

DR. ANDERSON: But did you gather more information on them after they dropped out?

DR. BURGE: Well, if they dropped out of the study, we no longer captured their data. Some patients may

have discontinued drug and stayed in the study to completion. We would have gathered that data but it would not have been used in our analyses.

DR. ANDERSON: Thank you.

DR. WILLIAMS: Fred? Dr. Weiss?

DR. WEISS: I'm appreciative of this discussion.

Just for the record, we do have further questions in questions V and VI, I think, towards the end, on the spinal mobility issues. Somebody raised that they hadn't seen it there, but we do clearly want to get into some discussion about the various ways to assess spinal mobility as well as long-term types of studies and long-term benefits and outcomes.

But just getting back to the first question and realizing that we asked in a somewhat very short and sort of general way, people started to comment a little bit about some qualifiers to that question about active disease or moderate to severe. I just want to know if we could have some further discussions.

Should this end up being licensed for an additional indication for ankylosing spondylitis, what kinds of thoughts do you have about the ways to qualify? You said active. Should there be some comment regarding failed other therapies, realizing that only NSAIDs are

really sort of the mainstay? If you can have some further discussion on that area, we'd appreciate it.

DR. WILLIAMS: Jim has suggested moderate to severe, and I've suggested active. So we'll have to hear from the rest of the committee, and I think it'd be hard to say we should have other agents that haven't been approved.

Mike?

DR. FINLEY: I don't know that I have the answer, but I do think we need to explore around the table the thoughts of whether the n that this will ultimately be exposed to is all comers who have AS but then beyond that a spondyloarthropathy and what the implications might be because currently, the only approved agents are NSAIDs, but we all, I think, can agree that although these have anti-inflammatory effects, these are not in the same category as NSAIDs.

DR. WILLIAMS: Gary?

DR. HOFFMAN: I'll just share some anecdotal experiences which hardly represents data but are strong beliefs on the part of a busy clinician. I don't think that we can always appreciate active disease as well as we think we do. I know this is true in many of the diseases we see in rheumatology. What we assume is inactive and burned out may in fact not be.

I make that statement in reference to this

disease because off label, I have prescribed etanercept for patients with spondyloarthropathy principally for peripheral joint disease to elderly people who I thought were fixed, fused and would have no benefit in terms of axial function and was quite amazed to see that my assessment of their activity in terms of axial disease was incorrect. They not only had less spinal discomfort but they also had increased spinal mobility and, as a result, had marked improvement in motion and function. So I think our usual parameters for assessing activity may, in fact, be fairly blunt instruments.

DR. WILLIAMS: Are you speaking against any modifier?

DR. HOFFMAN: Against any disease?

DR. WILLIAMS: It says ankylosing spondylitis, and Jim has suggested "moderate to severe" and I had suggested "active." Are you suggesting we not use any adjectives?

DR. HOFFMAN: I'm suggesting that we might not use adjectives but that patients who are disabled may, in fact, deserve a trial of therapy over a limited period of time and then have an opportunity to demonstrate improved function, quality of life, and if such does not transpire within a period of 3 months, for example, that then treatment be stopped and the patient be considered a

treatment failure.

DR. FRIES: I'm entirely in agreement with Gary. Looking ahead on the questions we're sort of anticipating when we're getting to the fusion exclusion, and I was thinking about that. I also would not include that because, first of all, there may be some surprises of people who seem to be fused but really aren't totally fused, and then there are other things going on in these people, even when their spine is fused. Their hips are getting flexion contractures. Their knees can be getting flexion contractures. They may be losing the ability to move their chest wall at all in terms of breathing or getting rid of hypostatic pneumonias. They may continue on with iritis and visual complications. So there are a lot of areas of the disease which are not even in somebody who was totally fused and you couldn't make improvement in those measures. I think that the drug still should be a way. So I would not put an adjective there.

Just to elaborate where my concern is, we got started 25 years ago looking at the epidemiology of ankylosing spondylitis with the blood donor studies where we looked at blood donors who were B27 positive and 1 out of 5 of them had what we began to term symptomatic sacroiliitis; that is, they met the New York criteria for ankylosing spondylitis but very few of them were diagnosed,

very few of them were receiving any treatment, and they were just going fine. In that paper, which was the striking prevalence paper in the New England Journal, the estimate was 2 million people. So that, at some level, there are truly a large number of people but most of those people aren't very sick at all and they certainly don't need major, major treatment.

I wanted to make the clinical point that all of the clinicians know but maybe people that don't see the patients don't know. Ankylosing spondylitis is very different from rheumatoid arthritis. The rheumatoid arthritis is a predictably progressive and so forth disease, whereas with ankylosing spondylitis, it really shades off towards these huge numbers of people with essentially trivial disease. So the issue that we're grappling with here is where on this area of symptomatology does the need for the availability of a powerful new agent exist.

I'm pretty happy with the way the trials were designed with regard to that question. In other words, you're going to design them to get a 20 percent change or an absolute value of 20 or things like that and that means you have to have an initial value of over 20 or you can never be in a sense eligible for the particular treatment.

So I think tacitly, if we stay as close as we

can to the patients that have actually been tested where the results are dramatic and accept the fact that several things will happen in actual practice as they have with other drugs, physicians who are running into a conundrum with somebody who couldn't have quite gotten into the study will use it anyway and the forms will be filled out a little bit pessimistically to get the third party payer to pay for it and all of these things will happen.

At the other end, if we're treating people that can't be helped by it, they're not going to have more than 3 months' worth of treatment. They and their physicians are going to decide that this just isn't going to work in these people.

So we're, I think, trying to define what we think would be a reasonable place, based on these trials and the Canadian thing and so forth, as to who we think the prime audience ought to be for it to be marketed to, reflecting the fact that the marketplace will shift that as time goes along.

It may very well do what the sponsor indicated, I think Dr. Burge indicated earlier, that it might take the scales off. It might set the bar higher. We might see more people that we think are indicated a year after it's on the market than we do initially just as we did with rheumatoid arthritis where we progressively moved these

drugs down earlier. It could happen again. I'm a little more skeptical.

But I think we ought to be cautious for a variety of reasons to not do what I'm increasingly calling extrapolation beyond the box; that is, generalizability beyond the bounds of the evidence-based data which you're going to use to justify these things. So that, if you're using the recommendations to justify treating people who were systematically excluded from the trial, then that's -- particularly when you know the direction of the problem; that is, they have less benefit to obtain on the low end than the people who are more active.

DR. WILLIAMS: Would you modify question I(A)?

DR. FRIES: Yes, I would. We could negotiate before we vote as to exactly how we do it. I would just like to tie it down to the evidence pretty much. I could be happy with "active" for its simplicity or "moderately to severely active" for congruence with the Canadian recommendations, and there probably are other recommendations being generated out there as well. So I would like to have some adjective for this low end.

DR. WILLIAMS: Other opinions on what that adjective should be?

DR. HOFFMAN: I think I heard Jim say two different things, that we were in agreement that it's

sometimes hard to appreciate what could be microscopically histologically active disease based upon our physical examination, and we know that acute phase reactants were only markers of reliability in half of the patients that were entered in the study.

So much like in a variety of rheumatologic diseases, this disease is not always transparent in terms of its more modest forms of activity, and sometimes you only realize that the patient was active after you've treated them and appreciated a considerable improvement. That, I think, would be part of the argument for not having an adjective in front of the ankylosing spondylitis indication.

Jim's other point, I think, was an important one, and that is, that if after 3 months of injections which have never endeared themselves to almost any patients, other than perhaps diabetics, there was no improvement, I think your patient would be loathe to continue treatment, if there was no objective improvement documented by the physician or subjective improvement or objective improvement in the eyes of the patient. So that would be the argument for not having the adjective.

DR. WILLIAMS: Mike?

DR. FINLEY: Yes. I would just concur with what Dr. Hoffman has said about the practicing clinician

recognizing active disease under the usual gestalt that we use, looking at things like acute phase reactants which in the data that's been presented, a lot of the patients were normal, even though once they got treatment, they went down to even lower normals on the range.

But if we think about what we do in rheumatoid arthritis and we look at trials, we talk about joint counts and MHAQs and those kind of things. In the data we've been looking at now, we're talking about occiput-to-wall and chest expansion, but I could see the notion that the typical clinician really kind of goes on their global assessment. The notion that most practitioners are in a busy practice measuring these kind of things on a regular basis to document results and efficacy, I'm not sure we do. I think we do some of the things that Gary points out. Someone comes in. Their spine -- we already kind of know what their spine is because of previous x-rays but yet they have a swollen peripheral joint. I think most of us would trend in the direction of let's give this newest tool in the toolbox a try. So I think as we go forward, and even though I'll be non-voting, my sense is that even if we put an adjective in front of it, it'll end up being used for folks who have AS.

DR. WILLIAMS: We are advisory to the FDA and they have heard what we've had to say. I think we will

vote on the question as written when that time comes, unless there's someone who has strong objections.

Question II has to do with subgroups that had less impressive response, including age, sex, HLA-B27 status, and psoriasis. The question is: Please discuss the significance of these subgroup findings, keeping in mind that there are few patients in some of these groups. That's II(A). I think we'll take that one first.

Well, let me go on. Question II(B). Discuss the effect of age. Older individuals had progressively lower responses given the apparent lack of treatment difference based on disease duration.

(C). If licensed, should the label describe any limitations in the ability to generalize the results to certain subgroups? Should the sponsor be asked to conduct additional studies in any of these or other subgroups you wish to identify should be further studied to evaluate efficacy?

(D). Patients with complete ankylosis of the spine were excluded. Should the label specifically discuss this population as one for whom safety and efficacy has not been studied? Should these patients be specifically studied?

Comments on these four parts of question II

I have a couple of comments. One is, when I

look at the B27 status, this population of patients included some other patients with spondyloarthropathies and were not ankylosing spondylitis. And I think the fact that the HLA-B27 group responded better, the other populations have a slightly lower percentage of B27 suggests that it's probably better in ankylosing spondylitis than it may be in some of the other spondyloarthropathies.

The other comment I would have is with age is that some of the deformities are fixed, and I think that those patients may be a little less responsive as they get older and that may explain some of the age differences.

But with psoriasis, it's already been approved for the use in psoriatic arthritis. It's being studied in psoriasis itself. The numbers were so small, I'd leave that to further studies of whether it has any benefit. That would be my comments.

Jim, you look like you have a comment.

DR. FRIES: Yes. This is a point of clarification because the study does include some people that don't have ankylosing spondylitis because we clinically at least use exclusions and if somebody's got Crohn's disease, we say they have Crohn's disease and associated spondyloarthropathy or something like that.

So if in fact this indication is going to be just for the words "ankylosing spondylitis", then I think

that it should be defined as that, and I think that will clean it up a little bit, and the other indications can be sought as Jim indicates they already are being in other specific kinds of instances.

This is a little confusing because the data, as presented, indicated with some pride, I thought, that it didn't exacerbate Crohn's disease. I mean, that's not like improving it. So it indicates that there might be different sorts of -- some drugs may be better in certain types of associated disease, bowel disease, for example, than others. So I would favor keeping this ankylosing spondylitis as the subject.

DR. WILLIAMS: Frank, then Gary.

DR. VASEY: I would just echo those comments and also Jim's comments about keeping the study to ankylosing spondylitis and not including the other forms of spondyloarthritis. We actually are doing a study on post-chlamydial reactive arthritis using doxycycline and rifampin and the data is preliminary but it looks encouraging at this point. So certainly if we could actually cure some patients with post-chlamydial reactive arthritis, we certainly don't want to be giving them etanercept instead of antibiotics.

DR. WILLIAMS: Gary?

DR. HOFFMAN: I'm also in agreement with Jim's

comments. In looking at the other parts of the question, although there were trends towards the older individuals not responding as well, they still did respond, and I don't think that would require any modification for a label.

And as far as generalizability to certain other subgroups, I think again there are real limitations in the smaller numbers of individuals in each of those subgroups, and I'd be hesitant to indicate anything on a label that would suggest that that data was robust.

And as far as part (D) to the question, complete ankylosis of the spine, I think that is a presumptuous assumption when you look at that radiographically. I don't know that if you were to look at that anatomically at a postmortem that you would in fact demonstrate that complete ankylosis radiographically is in fact what is true anatomically, and so I would not exclude that in the indication because of personal clinical experience, that suggests that even people who appear to be ankylosed may not be and may still derive benefit in terms of axial symptoms.

DR. WILLIAMS: I think you make a really good point in the fact that even the subgroups that didn't respond quite as well responded, and if that had been the response for all the groups, we'd still be talking about it as an indication for ankylosing spondylitis. So I agree

that even though some of the subgroups didn't respond as well, they shouldn't be excluded, and you've already discussed earlier some of your thoughts about ankylosis which I think are appropriate.

Jim?

DR. FRIES: Just that I agree with the need not to take age into account. To me, it's like the total fusion issue. You don't know it until you try it, and I'm in favor of being totally liberal toward the severe end of this disease. My concerns are all at the other end because there's a lot of varied manifestations, and the age effect, particularly when I'm well into the upper group, I get attacked at Stanford when we say anything about using age as a criterion because, of course, age is different things to different folks. So anything you put in, you'll have the AARP all over you, and so I'd favor leaving that one alone.

DR. WILLIAMS: Jennifer?

DR. ANDERSON: I'd just comment about in D, there's this additional question, should the patients with complete ankylosis of the spine be specifically studied, and we've heard Gary's personal experience, and I think it would be a good idea that they be studied in a trial, in addition to one set of experiences.

DR. WILLIAMS: Mike?

DR. FINLEY: I'm just wondering and perhaps it's my naivety in being new to the committee and the discussion and other committee meetings about etanercept, but the subgroup of women and their spondyloarthropathy in AS is, I think most us appreciate, different than in men. Maybe I'd ask the sponsor, but also, these are young people that get these diseases. Thinking of Jim's point about the low end of the spectrum and the notion of pregnancy and some other things that perhaps we haven't really talked about publicly but is still there, I might wonder what the people feel around the table about that and maybe hear from the sponsor.

DR. WILLIAMS: Frank, do you have any specific comments on that?

DR. VASEY: No. I would only say on the issue of mild disease, I think what we're really talking about is people who have failed non-steroidals basically. I'm not sure if we could directly put that in the language, but I think that's really what we're talking about.

DR. WILLIAMS: What do you think about the differential response from men and women?

DR. VASEY: I mean, we've always talked about the fact it was a milder disease in women and that's why it was so much more infrequent. Other than that, I really can't say very much. I don't know actually if it's a

milder disease in women. We've seen some severe disease in some women.

DR. WILLIAMS: Dr. Burge, did you have any comments?

DR. BURGE: No.

DR. WILLIAMS: I would make a comment on Jennifer's thoughts, and I agree with Jim and Gary that I don't think ankylosis should be an exclusion, but I agree that it ought to be a group that ought to be studied because it should be an answerable question.

Dr. Weiss, and then Dr. Siegel.

DR. WEISS: Both Dr. Anderson as well also said that, in answering that second part of (D), that it should be studied. Can you expand a little further on what you think? Partly because oftentimes when you approve something, it may be difficult, depending on what disease you're talking about, to actually enroll patients in a -- if you're talking about a placebo-controlled or add-on placebo-controlled trial, you've also maybe got the added issue that if you're talking about people with complete or more severe forms of spinal fusion, that you might need to be treating longer and then that necessitates how long and what kinds of controls to use.

So if you could just maybe expand a little bit on what you think might be optimal ways to try to study

this topic?

DR. FRIES: Could I ask you to clarify it in turn? Because obviously it's the easiest thing in the world to call for more research, and we all want more research. We want to do more research. So the question is, with regard to the FDA's relationship with the sponsor, would you see suggested areas as ones which you would encourage as areas for post-marketing study by the sponsor, or whether the sponsor would be asked to consider going for a different indication, such as the disease-modifying indication or something like that? I mean, how would this take effect? You're not suggesting that we would do additional studies now prior to approval?

DR. WEISS: No.

DR. FRIES: Okay.

DR. WEISS: The other options, as you said, many of these can be part of post-marketing commitments, if they're feasible studies to do. I mean, again we all run to the habit of asking for things because there's just a lot that we'd like to see, but the question is what's practical, what's feasible to do, what's appropriate, and what kinds of settings. Post-marketing is a very common arena to try to evaluate other related aspects of disease.

There's also the whole issue about claims, about perhaps being able to achieve a claim that's more

than simply a signs and symptoms kind of claim and what that would entail.

DR. WILLIAMS: I am a strong advocate of placebo-controlled trials, but I think in this case, when we're talking about ankylosis, they've already demonstrated that etanercept works on ankylosing spondylitis. I just think you study a population of patients who have ankylosis by x-ray and see if they get a similar response. I don't think it needs to be a placebo-controlled trial.

DR. FRIES: Yes. There are a lot of careful designs, and I hesitate to throw out things that haven't been thoroughly thought through and vetted. Obviously I'm always in favor of long-term studies, and I do note that in 24 weeks, there are substantial measurable effects on aggregate infections and so forth, even with a really short time period. I'm not sure that there's an endpoint for when you would stop treatment with Enbrel in ankylosing spondylitis. So you might be talking about 20-year courses if something else didn't come along in the meantime, but some long period of time. So when you're talking cost-benefit/cost-effectiveness, you really have to figure out what's happening to these rates, I think, over a longer period of time, so that you can actually project what the answer is. And it's in that area that some of the subgroup analyses are attractive to me.

For example, I liked the presentation of the age data, even though I don't like the use of calendar years of age, but it does suggest what you would normally expect, that the older the patient population that you get, the attendant co-morbidity, that decreased host defenses, the increased damage as opposed to inflammation in the disease process, that your effectiveness is likely to trend toward getting worse at the same time that your toxicity is going to trend toward getting worse. So that, you have a decreasing effectiveness and you have increasing toxicity. So that is an area where we're trying to make an argument, which I think they make very well here, the sponsor makes very well here, for this group of patients, but you're going to say, well, at some point, there's going to be some area where you want to become more enthusiastic.

The same thing happens as you go down the scale with regard to disease severity, which is why I've been harping on that so much, because the amount of gain goes down as the amount of disease to be treated goes down, and as the difference between the NSAID treatment and the new drug, because the NSAIDs are perfectly fine -- the patient only takes them on Sundays, doesn't really seem to need anything -- you're going to have inevitably, as you go down the scale toward milder disease, less effectiveness and you should have constant toxicity so that the ratio is again

going to shift as you move down there.

I would think that in light of this, I'll be talking for an adjective there, but I think that the sponsor should be encouraged to consider going to populations which would not have met the criteria for these trials and for an amended thing or something if data came on that you could make a similar kind of benefit-risk ratio argument in people who had milder disease than those who are studied in these trials, then bring that in at a later point. And I would encourage the doing of such a study. It might work.

DR. WILLIAMS: Other comments on Dr. Weiss' question? Dr. Siegel, you had a comment?

DR. SIEGEL: Yes. I just wanted to make a clarification. The issue was raised about the patients with concomitant psoriasis, and Dr. Williams mentioned that etanercept is approved for treatment of patients with psoriatic arthritis.

Please do keep in mind that those studies in psoriatic arthritis were specifically including patients with peripheral joint involvement and patients with exclusively spondyloarthropathy were not included.

In addition, patients who had spinal involvement but also peripheral involvement, the spinal involvement was not studied. So we don't really have any

information based on those studies for that approval about spinal involvement.

I also wanted to ask a question. Several members of the panel have mentioned that this should be used for ankylosing spondylitis and not the other related spondyloarthropathies. Can you comment on whether you believe that there is efficacy demonstrated in patients who meet New York criteria for ankylosing spondylitis but who also have these other concomitant conditions because they were included in the trial, of course?

DR. WILLIAMS: I don't think the numbers were adequate to make those decisions. I think that they've clearly demonstrated ankylosing spondylitis. I think that it probably will work for the others and it'll be used for the others, but I don't think that the data is as convincing for the others.

DR. FRIES: I think Gary's point about reactive arthritis maybe needs an antibiotic approach first. I mean, there's different sequences for the different drugs, and there's reason to think you might have paradoxical results, I think, in some of those. There's already some evidence in this class that ulcerative colitis and Crohn's disease have different responsiveness to these agents, and I wouldn't have expected that a priori but that's where the data seemed to be going.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: And along the lines of the earlier discussion, would you recommend any qualifiers with respect to the people meeting criteria for this trial but who had those concomitant disorders?

DR. WILLIAMS: I personally wouldn't mention the other disorders. It's going to be used for them anyway, whether or not you approve it today, because of the data that's come out. But I think that until there's stronger data, I wouldn't mention them.

DR. FRIES: Most people that are practicing make the exclusions. As I indicated before, they talk about it being Crohn's disease with spondyloarthropathy or something. So I think if it just says ankylosing spondylitis, I don't think you need to further define that for the busy doc. I'd like to keep these as simple as we can.

DR. WILLIAMS: Jennifer?

DR. ANDERSON: I'd just like to go back to this question of possible additional study for patients with complete ankylosis of the spine. I don't have any clinical knowledge on this, so I don't know whether there are degrees of "complete ankylosis" that can be assessed or whether it's just all or nothing, so that if their state could be measured at baseline, that would be a helpful

thing to do.

Also, I was just curious to know what proportion of patients with active spondylitis or severe spondylitis are in this situation of being termed having complete ankylosis.

DR. WILLIAMS: Frank?

DR. VASEY: Well, in my experience, I'd say it's a minority, maybe 10 to 20 percent, something like that. The disease certainly does progress, I think, somewhat predictably but slowly and some patients never seem to fuse. So I think that's some of the imponderables in trying to decide how to manage it basically.

DR. WILLIAMS: I'm assuming you're saying 10 to 20 percent of those who have recognizable disease because there is a vast population of ankylosing spondylitis who never get seen by a doctor.

DR. VASEY: Right. I'm just talking about the ones I see.

DR. WILLIAMS: Gary, you had a comment?

DR. HOFFMAN: I think it would be a very difficult study to do in terms of recruiting. I think it'd be very expensive, and I'm not sure that it would change the use of the drug. I think we'd use it very much the same way as the indication would now be written.

I'd just make one other point that I find kind

of fascinating, and that is, from the few patients that I've had that I've thought were fully fused, who've seemed to function so much better, even though I initially treated them for their peripheral arthritis, I think that the improvement that they may be having in their spine is certainly not just what we measure in a Schober's test, and if they had another 5 or 10 degrees of motion in their lumbosacral spine, another 5 or 10 degrees in their thoracic spine, that may not be measurable using the tools that we apply to their back with the tape measure. It may be something that is more subtle than our clinical perceptions but certainly not subtle to the patient who now can function a lot more effectively.

DR. FRIES: I would just make an extended comment with regard to the epidemiology of ankylosing spondylitis which is very poorly understood, and I think we don't know really how many cases there are because that's a definitional kind of issue. We don't know what the natural history is now and how that natural history varies from what it did 30 years ago.

Those of us who've been around treating these folks for a long time are impressed that in our clinics, even our VA clinic, we don't see people that look like that picture, that everybody used to look like that, and there are big clinical debates about how you would cut the neck

and sever the vertebrae and straighten that thing out and they are things that we never even think about doing now. To me, that's always seemed to be the best argument, that maybe the NSAID era has actually done something despite the dearth of positive data from trials that would lead you to believe that. But for some reason, we have actually been doing a little bit better. Gary would probably agree with that.

DR. WILLIAMS: Jennifer?

DR. ANDERSON: Just something about what you said about more subtle changes in the spine and spinal mobility that aren't measured by Schober's test. Are there other measures or could they be developed that would be better ways of assessing what's happening in the spine or what could happen in the spine?

DR. HOFFMAN: I think you get a little better idea of complete spinal mobility, including cervical mobility, when you do the occiput-to-wall measurement. I think you might be able to pick up something there in someone who you thought was fused and actually was developing some subtle signs of improvement.

I'm just questioning whether a whole other study to demonstrate improved spinal mobility in what is an increasingly rarely-appreciated subset of people is really worth the investment of time and money.

DR. WILLIAMS: Mike?

DR. FINLEY: Yes. I just would expand on what Gary said. I think it still comes back to what clinicians will do in the office, and I suspect that even if that trial were done, the notion that people are getting out their measuring tapes on a consistent basis to do things beyond the Schober's test, I'm not sure they are, and I suspect that once someone is defined as having a spondylitis, AS or not, they would be considered as a candidate for things like etanercept.

DR. WILLIAMS: Further comments on question II?

Let me just summarize as I think I've heard it and then you can tell me if I've summarized it correctly. Please discuss the significance of these subgroup findings, keeping in mind that there a few patients in some of these groups. And we determined that there would not be much to say about the subgroups.

Please discuss the effect of age. And those of us who are older felt that that was inappropriate.

(Laughter.)

DR. WILLIAMS: If licensed, should the label describe any limitations in the ability to generalize? And we said generally no.

Should the sponsor be asked to conduct additional studies in any of these groups? Again, we

didn't feel that was necessary.

Lastly, on ankylosis of the spine, we felt it should not be listed as an exclusion, and we were somewhat divided on whether further studies would be of benefit.

Have I reflected your comments accurately?

DR. FRIES: Well, Jim, I think that we did suggest -- most of those were, I think, sort of consensus questions, but I raised the issue of whether a study in milder disease should be considered. I think several of our comments indicated that perhaps a non-randomized post-marketing surveillance follow-up into a period of time that you couldn't maintain placebo anyway in folks should be done. I think it was implicit that it might be fun to kind of put in some radiographic changes if one were going to try and get experiences that went out for 5 years. I think it would be important to know whether there were cumulative toxicities or toxicities that we haven't yet recognized.

So I think there were some things that I heard I thought we suggested.

DR. WILLIAMS: Wendy?

MS. McBRAIR: Also, we should continue to look at or really begin to look at quality of life and work disability and physical function. I think the sponsor has done a good job of keeping contact with the other of their study participants for rheumatoid arthritis, and I would

hope they would be able to continue that as well with the AS group.

DR. WILLIAMS: Dr. Siegel, any more you need on this question?

DR. SIEGEL: No.

DR. WILLIAMS: We'd then like to turn to the open hearing, and our first speaker will be Jason Crispin. You can use the microphone right there.

MR. CRISPIN: If it's all the same to you, I'd like to come to the podium.

Good morning. Please bear with me. This is the first time I've ever actually spoken about my condition in public. So I'm a little nervous. So just bear with me.

Anyway, my name is Jason Crispin, and I don't know. I appreciate the opportunity to talk to you about my experience with Enbrel.

I was diagnosed with ankylosing spondylitis when I was 15. I'm 23 now, and I've been on Enbrel since 1999, since March of 1999, so not very long after it had been released for the public.

So let me give you a little bit of back story about my condition, what exactly led up to me being diagnosed with ankylosing spondylitis, so you can have a little bit of history about what I've had to deal with in my life.

So when I was 10 years old, I began to study tae kwon do, and I took classes three or four times a week for about four years. And during this time, I developed an injury which was first diagnosed as a torn muscle in the groin area, and after resting and rehabilitating the damaged area, I returned to my martial arts program. Unfortunately, this wasn't the first occurrence. The injury continued to occur and it would just come and go.

When I was 13 years old, I basically got so bad that it felt like both of my hips had been broken, and I had to walk around on crutches. I was just in excruciating amounts of pain. I think it had to have been the worst amount of pain I've ever experienced in my life.

So my general practitioner told me that I'd simply redamaged the area again, been more widespread this time, and that I was just going to have to lay off doing the kicks and such until it got better. It got better after about three weeks. I seemed to recover completely.

I had an MRI taken at the time, and, unfortunately, because I had difficulty staying in one position at one time because I guess I got a little bit claustrophobic, so it was a bit -- so, the study unfortunately -- the MRI didn't show what exactly it should have showed at the time and it was inaccurate.

After about a month, I noticed I would be stiff

in the mornings in my hips, and also I had developed chronic back pain and pain in my shoulders and neck. So I would seem to go through episodes of it. They would last from like 2 to 19 days and it would cycle through, depending on the season, depending on the stress in my life at the time, things like that. My hips would become so swollen, that it would inhibit my ability to walk. I would limp around.

I gradually began to lose interest in my pursuits of studying tae kwan do because I could no longer get the kicks up to head level and my agility and mobility suffered because of it, and I was just horribly sore after every practice as well. So it just got more difficult and finally, when I was 14, I lost interest completely. I mean, I don't know.

I had to take 2400 milligrams of ibuprofen a day from 14 on basically. So I was on a fairly high dosage. Who has to do that when they're 14 for the most part, you know?

So the symptoms of my condition continued to get worse. A friend of my mother's finally recommended that I be taken to an orthopedic surgeon. This was later right when I was about to turn 15, and I went there and I went to see a Dr. Leo van Herpe, a very prominent physician out of Arlington, Virginia, and he diagnosed me. After

taking x-rays of my hips, he diagnosed me with bilateral slipped capital femoral epiphysis in both hips. He prescribed Indocin for me.

Basically what happened is it had not been found and since it hadn't been found, it had healed itself because normally surgery is indicated as soon as they find that, but since it fixed itself, I have spurs in my hips and it's definitely given me a lot of problems in the past. He prescribed Indocin for me to help relieve the swelling and pain in my hips.

A couple of months passed and my problems went into remission. My symptoms were obviously noticeably reduced, until the prescription ran out. When I went in for my follow-up visit, I explained to the doctor that my condition had just gotten worse after I had stopped taking the medicine but while I was taking the medicine, it was helping.

So he then recommended that I would go to a rheumatologist. That's where Dr. Patience White came into play. She was a very well-known doctor out of George Washington and Children's Hospital, and I went to her and she diagnosed me with ankylosing spondylitis.

From this point, here comes the really fun part. After this, I got prescribed medications, and I was never on anything less than eight or nine medications at

any one time. So nothing seemed to really help after this. My disease continued to decline. I had to take physical therapy for months at a time to try to continue with the fight that I had against myself and my body to just retain my mobility. Things that taken for granted for kids my age, I mean, I really had a lot of difficulty in continuing to function as a normal human being.

But anyway, prednisone. Prednisone was something that helped a lot. I would take prednisone and I've been on prednisone since I was 15 and 5 milligrams a day now, but back then, it would be up to 25 to 60 milligrams at times and then usually no less than 10 milligrams.

So unfortunately, this gives you a bad -- I don't know if you -- I'm sure you all are familiar with side effects the prednisone gives, but the prednisone gives you a rather bad rash or bad bouts of acne on one's face and on their chest and that, in combination with this limp I had, ostracized me from my school. I basically withdrew from all social interaction and was very depressed and my physical health ruled my mental health.

I think I was about 16 or 17. Dr. White became semi-retired from practice, and I was recommended to go to her former student Dr. John Trowbridge, but I started also to exercise in high school. I started to take a weight-

lifting course, and by the latter half of the first semester, the fall semester, I had blown out both of my knees weight-lifting and they had begun to swell horribly to the size of balloons. I got them drained repeatedly. Nothing seemed to help with that.

Finally, I went to an orthopedic surgeon. It was recommended that I go and have partial synovectomies done on both of my knees and that helped for a couple months. Unfortunately, the swelling started again and it just continued to be a roller coaster basically, just getting worse, progressively going down.

In 1998, when I was 19, Dr. Trowbridge talked to me about this new medication on the market called Enbrel. There was only one drawback. Enbrel was not indicated for my condition, but Dr. Trowbridge was determined to get me put on Enbrel, and after a long fight and he also had to change my diagnosis from ankylosing spondylitis to also rheumatoid arthritis as well, so I could be within the indicated bracket to get the medication. And after a long fight with my doctor and myself against my insurance company to pay for the medication, I was finally allowed to try Enbrel. And let me tell you something. I noticed a difference, I believe, within the first 48 hours of being on the medication. I was starting to almost instantly feel better.

It's been four years now since I've been on Enbrel and I got to say everything has been a lot easier since I started on Enbrel. I mean, I can remember a time where after I would go to work all day, between work and college, I had a lot of stress in my life, and I would have to stand at my job for 10 hours a day, and sometimes after I got off of work, I would have to be helped in. My mother would have to bring out my crutches to get me out of the car and then I would hobble in. And it was definitely not something that anybody would want to deal with.

As far as since Enbrel, though, I have been able to take control of my condition. I have been exercising for the last two years. I can run 5 miles now. I can jog it, and I've stared taking tai chi. I have now completed my associate's degree in liberal arts, and I'm working on my second associate's degree in radiography. I have a lot more friends than I used to and it's opened up so many doors for me that I don't think would have been opened at all for me if I hadn't been able to get this medication.

So I've been able to study tai chi, and I've regained so much of my flexibility that it's unbelievable. It completely reversed the fusing process that was already beginning with my spine and certain areas of my hips, and yes, so definitely not so bad. I mean, while it's not a

complete recovery, I still have flares, I like to call them, times where my disease is active and it does hinder my ability to move around, but it's not nearly as frequent or as severe as it used to be. So I definitely would say it's a success story all in all.

I'd like to close with this. Dreams are the reason we keep going. Without them, we lack identity. Before Enbrel, my dreams were stripped away from me slowly every day for eight years while I struggled every day just to be a human being. What is taken for granted by many had become an everyday struggle and frustration to endure for the next day. With Enbrel, I know I now have a chance to be somebody, to further my quality of life and to better myself.

Just this last month, I have been to New York to model for Amgen in two separate professional photo shoots to advertise for the company. It was a thrill. It was great. I had a ball.

I have a close circle of friends. I have a steady girlfriend and all of these dreams of a future that I currently strive towards I don't think would have been possible if not for Enbrel. I only hope that some day my motivations and goals to fight my disease will help give strength to others with my problem, with my condition, and with my actions today, so they may receive the same

opportunities that I have.

Thank you very much.

DR. WILLIAMS: Thank you, Mr. Crispin.

Are there any questions for Mr. Crispin? I have to ask you one question, and that is, you told us about the photo shoot. Do you have any other financial support, including travel expenses, or any financial interests in a pharmaceutical company?

MR. CRISPIN: Well, everything was paid for for the shoot by Amgen, and I got paid for it.

I work at a restaurant right now full-time. I'm a waiter/expediter of food. My actual job description is to prepare dishes to be sent out for the servers and then take them out during the busy peak times of business, and yes, it requires me having to carry the big trays like this or like that. I mean, I don't know. I'm able to do a lot of physical activity and I'm fine with that.

I study hard at school. I go full-time. So I'm getting close to finishing that degree. I got the end of the tunnel in sight.

DR. WILLIAMS: Were you paid to come here today?

MR. CRISPIN: No, sir.

DR. WILLIAMS: Thank you very much, Mr. Crispin.

Our next speaker will be Jane Bruckel, and I would ask the same questions of you, Ms. Bruckel.

MS. BRUCKEL: Hello. I'm Jane Bruckel. I'm a registered nurse. I'm a founder and executive director of the Spondylitis Association of America, and I have ankylosing spondylitis, and I'd like to thank you for giving me the opportunity to speak today.

And to address your question right up front, I'd like to disclose that the Spondylitis Association has never received funds from Amgen but we have in the past received funds from Wyeth for various projects, and my husband and I jointly own a 158 shares of stock in Amgen that we bought as Immunex back in June of 2000.

For the past 20 years, the Spondylitis Association has been the only non-profit organization in the U.S. focusing all efforts and resources on ankylosing spondylitis and related spondyloarthropathies. Our mission is to improve the quality of life, promote early diagnosis and effective treatment and support research that leads to a cure.

AS affects at least 300,000 people in this country but thought leaders believe the true prevalence may be as high as rheumatoid arthritis. Recently, the Spondylitis Association took a leadership role in developing the guidance document on AS that has just been

submitted to the FDA this month, and I'm on the committee that has just developed guidelines for the use of biologics in the treatment of AS.

I come here today to speak passionately about Enbrel and the new biologics in general. As you can imagine, there's been a lot of discussion about the biologics on our web site bulletin board, and before I share my personal experience, I'd like to read several typical testimonials from over a hundred of those discussions on the bulletin board from this year alone.

"This past weekend, before I started my first injection, I was feeling worse, more so than I have in a long time. I told myself this is it. I have to try it. I can't live like this. What kind of quality of life is this if I'm not enjoying the best I can? After the first injection, within the hour, I noticed a difference. By that night and the next morning, I felt great and continue to do so. I know I'm fortunate that it's working so soon for me as I've read that it doesn't for everyone. The biggest thing I've noticed is no more fatigue. I'm starting to feel like I have my old self back and I haven't seen her in four years."

Here's another. "I dragged my feet when it came to starting Enbrel and now that I did, I promise you this, it will be worth it. First of all, I started

noticing relief after about three weeks. Some people notice faster and some people take a little longer. I can tell you for sure when you do notice it, it'll be like you wake up one morning and go, wow, I just slept through the night.

"One of my biggest fears is that it will be taken off my insurance company's list. I live in constant fear of that or that I might lose my insurance. I don't think I could go back to living with the pain again and at a thousand dollars a month without insurance, this is definitely not possible for a lot of folks."

And then this one. "My insurance will not pay for Enbrel because it is currently not approved for ankylosing spondylitis."

My experience sort of starts through the experience of a co-founder of the Spondylitis Association who has severe AS. He has spinal and peripheral involvement. He's disabled, uses a cane and even has to use a cart to get around. In early in the year 2000, he called me to say that he had started Enbrel and what a difference it was making in his life and he urged me to give it a try.

Like many people, I procrastinated for a long time because of concerns about the potential problems being an unknown drug, being new, reading things that sounded

very scary, and so I just kept putting it off. But by December, I felt I needed to do something.

Now, my spine is completely fused, except for my neck, and I assumed that the feeling of stiffness was due to my fusion. I also had some pain and both my doctor and I assumed that that had become more of a mechanical cause of the pain rather than the inflammatory nature of pain that I used to experience, but within a few weeks of starting Enbrel, I gained such freedom of movement. I felt like a kid who couldn't wait to run outside and play.

In the beginning, I was so giddy with this excitement that I would show off my new freedom of movement at every chance I got. I mean, at work, I took all my co-workers out into the hall and I showed off how I could run up and down the stairs, and when taking a walk in the neighborhood with my husband, I started to run down the street and hop up and down the curb. I left him in the dust a block away. I don't run gracefully but now I can run, and on New Year's Eve, when we had guests at our house, I couldn't help but show off how great I felt. So symbolically, at the stroke of midnight, I got out a jump rope and I started to jump.

I've been on Enbrel ever since. It has truly given me my life back. I'm totally symptom-free. Biologics may not be as effective for everyone, but they

are definitely a breakthrough in the treatment of AS, and I urge the committee to approve the application for Enbrel for AS.

Thank you.

DR. WILLIAMS: Thank you.

Are there questions for Ms. Bruckel?

(No response.)

DR. WILLIAMS: Thank you very much for coming.

DR. FRIES: Jane, how long have you been on Enbrel now?

MS. BRUCKEL: Since December of 2000.

DR. WILLIAMS: Other questions?

(No response.)

DR. WILLIAMS: Thank you, Ms. Bruckel.

Now that we've had the open forum, if we could go back to question I, and we will take a formal vote of the committee. I(A). Do the results from these clinical trials demonstrate that etanercept is effective in patients with ankylosing spondylitis?

Those voting members in favor, please indicate.

(A show of hands.)

DR. FRIES: I don't think anybody wants to vote no on anything, but I really do need to have something that keeps us within the bounds of the trial patients. So I do ask that we have an initial question as to whether we

insert the word "active" and so forth in that.

DR. WILLIAMS: But we discussed that earlier and decided not to, but if you'd like to discuss it again.

DR. FRIES: Well, I don't really want to add anything to the argument, but as I read the question without the word in there, then we're going to have a split vote, at least in some way, and I would prefer that we have a consensus of the committee.

DR. WILLIAMS: I just was going back to the previous discussion where we discussed whether we should put a modifier in and decided not to. Are there those who would like to put a modifier or adjective in front of it, other than Jim?

(No response.)

DR. WILLIAMS: So we'll leave the question the way it is.

We voted. You're the only one that hasn't voted. You vote no?

DR. FRIES: I vote no.

DR. WILLIAMS: So 5-1.

Question (B). If licensed, do the data support an indication for reducing signs and symptoms? I assume that's for ankylosing spondylitis.

Those of the committee in favor?

(A show of hands.)

DR. WILLIAMS: And opposed?

(No response.)

DR. WILLIAMS: That was 6-0.

This is probably a convenient time to break for lunch. We have an hour for lunch. So we will return at quarter to 1:00 and resume with question III.

(Whereupon, at 11:45 a.m., the committee was recessed, to reconvene at 12:45 p.m., this same day.)

AFTERNOON SESSION

(12:50 p.m.)

DR. WILLIAMS: We're ready to reconvene this session, and the committee will now move to question III.

Just to introduce the question, I'll read just a portion of the preamble. Safety data from the three controlled trials in general revealed a similar pattern of adverse events compared to what is already known about etanercept. In study 1, the largest study, there appeared to be an imbalance in the number of etanercept recipients who were withdrawn from the study because of new or recurrent inflammatory bowel disease. 2 withdrew for inflammatory bowel disease symptoms: 1 newly-diagnosed and 1 recurrent.

Section A. Please discuss whether the data suggest an adverse effect of etanercept on exacerbation of inflammatory bowel disease. Should there be further evaluation of the potential for etanercept to exacerbate inflammatory bowel disease? If so, given that inflammatory bowel disease is associated with AS, what kinds of study designs would be best to address this issue?

B. Should further studies be designed to assess the impact of etanercept, both positive and negative, on the other non-skeletal manifestations of AS?

I think we ought to take those as two separate

questions and let's first deal with III(A), which has to do with the inflammatory bowel disease and adverse events seen in study 1, 1 patient with re-exacerbation of the disease and 1 with a new diagnosis. Do we consider that to be a harbinger of adverse events?

Frank?

DR. VASEY: I was pleased that the company addressed the issue because it was known that the studies of inflammatory bowel disease were negative but at least there was no exacerbation. So I was reassured by that.

DR. WILLIAMS: Jim?

DR. FRIES: I think this falls in that general category of things that ought to be counted in one way or another as things go forward with a new indication and we find out if it's something. I can't get at all excited about two events here, one of them pre-existing, either, but I'd keep an eye on it.

DR. WILLIAMS: I certainly agree that two events didn't make catch my interest very much, but I think it's worth post-marketing surveillance or looking at other studies. The other studies were all negative.

Dr. Weiss?

DR. WEISS: One of the problems with post-marketing is just that if you start to see exacerbations which people with pre-existing IBD, of course, will have or

people will become diagnosed with IBD over time, it's going to be very difficult without a comparison, unless there's good data out there, which there probably isn't, -- I'm sure there isn't any kind of information, though you can correct me if I'm wrong -- about these concomitant other types of inflammatory conditions. You won't be able to know whether or not this is somehow making it worse or increasing the numbers in a post-marketing setting.

That's why you said keep an eye on it, and maybe you could clarify what you mean by that.

DR. WILLIAMS: I think that the data, the negative studies with etanercept on inflammatory bowel disease, specifically Crohn's disease, is comforting in that it did not cause an exacerbation of the inflammatory bowel disease and this was a population of patients with inflammatory bowel disease.

The study we did here today did have a mixed bag in that you had some patients with other forms of spondyloarthropathy, including, we assume, some with inflammatory bowel disease. I think it's hard to draw many conclusions from this study when everything else has been negative. I'm most comforted by the fact that the studies of inflammatory bowel disease didn't show an exacerbation.

Jim?

DR. FRIES: Yes. I wasn't specific for exactly

the same reasons that you enunciated. It's hard to figure out how to do it. I think for signals, you can probably look at spontaneous reporting and see if they pop out, particularly if you have an infliximab reporting concurrently situation. I don't know if that's in the cards or not.

The other thing was that Desiree and I were talking during the break about how you would do an outcome study and get radiographic outcomes in and you'd also like to count infectious hospitalizations. There are a whole lot of things that came along that you really could figure out for sure in a 4-year study or 3-year study what they were, and including if you did the design right -- and it would have to be mostly quasi-experimental -- you could determine the effect on bony erosions.

The reason I say quasi-experimental is that you're only going to be able to run your placebo group alongside for maybe 6 months or so, possibly a year. Otherwise you just won't be able to hang on to them no matter what you do. So you're going to be following your cohort which can be part of a post-marketing surveillance thing rather naturalistically and use your shorter-term placebo controls as your hard reference and then your expectations for the individual people using estimates of progression and severity of disease and models for

individual patients in order to put them in.

In other words, I think there are designs, and if in fact the company and you and everybody decides to go in the direction of answering some of these questions for the company, it would be very good to get an indication for disease modification, and if you can negotiate something that would be satisfactory evidence, then they might be encouraged to do that. And if you did it, then you would just load it up -- it wouldn't be hard to load it up -- with counting exacerbations of inflammatory bowel disease, looking for the serious infectious endpoints, looking for anything else you have you would just build into that prospective surveillance.

So I think it would take some imagination in order to do it, but I do think you're going to want to get longer-term data for several variables.

DR. WILLIAMS: Gary?

DR. HOFFMAN: I think a piece of data that we don't have that is very relevant to the IBD question is if you were to have a cohort of 270 patients with ankylosing spondylitis who did not appear to have IBD but realizing that some people with IBD present first with their musculoskeletal disease is 1 out of 270, about what you would expect to see becoming evident in the course of following that cohort of patients, and if it is, then there

really is no signal here at all.

DR. WILLIAMS: It's probably better for Frank to answer this, but wouldn't you think the one out of 270 is probably fewer than you'd expect?

DR. VASEY: I agree. That's actually one of the surprising things, is that this drug doesn't seem to work for inflammatory bowel disease. Based on the studies in ankylosing spondylitis from Europe of colonoscopies in asymptomatic people in which they find patchy inflammation of the colon, I was sort of interpreting it as one big disease with inflammatory bowel disease at one end and ankylosing spondylitis at the other and everybody else sort of in between, but this observation would seem to negate that. Maybe it is a different disease somehow.

DR. BURGE: I was just going to comment real quickly. If you'd pull the slide up. If you recall, for the new inflammatory bowel disease, there's actually one patient newly diagnosed both in the placebo group and in the etanercept group. So if you want to take your placebo group as your control there, you can see that it looks like it is as expected.

DR. WILLIAMS: Gary?

DR. HOFFMAN: Right. That was the data I was referring to, and I think that data more than anything else is fairly convincing in there not being a case to be made

for causation.

DR. WILLIAMS: Further comments? If I were to summarize this question, we would say that at least the committee doesn't have a great deal of concern about what we've seen and don't have any suggestions on how you'd monitor it further.

The second part of that question III. Should further studies be designed to assess the impact of etanercept on other non-skeletal manifestations of ankylosing spondylitis?

Since no hands are up, let me just make a comment. I think this is always difficult. We have the same problem with rheumatoid arthritis in the nonarticular manifestations and that's getting enough patients to get a meaningful study, and I would think the only way you could do it is to pick out what particular manifestation you're interested in and design a study which would have to be multicenter to get enough patients. It would be very expensive and time consuming just to gather enough patients.

The one area I think they may be able to do is in peripheral arthritis where they could get a significant number of patients over a reasonable period of time, but many of the other manifestations are so infrequent, that it would take a long time to collect enough patients.

Others have other comments? Frank?

DR. VASEY: Yes. The iritis is about 20 percent and that is self-limited for the most part. It seems unlikely that that would be an indication for the drug very often, and upper lobe pulmonary fibrosis, amyloidosis, seemed to be unusual in my experience anyway.

DR. WILLIAMS: Dr. Burge?

DR. BURGE: If you'd like to see iritis data from the clinical trial, we can pull the slide up. There were a good portion of patients in the study that did have iritis/uveitis at baseline, and as you can see, they were pretty well matched between the two treatment groups across the studies. There were 9 flares of uveitis/iritis, in the placebo group compared to 3 in the etanercept-treated patients.

DR. WILLIAMS: So in the placebo group, you had 9 flares in a 140 patients over 6 months. That would take a long time to get a significant number of patients. Iritis is not the most common but it's one of the more common manifestations of nonarticular, nonskeletal ankylosing spondylitis.

Mike?

DR. FINLEY: I would just ask Dr. Burge. Was that baseline just by self-report of history or were they actually having manifestations at entry?

DR. BURGE: These were not patients that had manifestations at entry. This was history of uveitis.

DR. WILLIAMS: Other comments? Dr. Weiss?

DR. WEISS: This is fine. We wanted to clarify because there's sort of two things we were looking at. One is whether or not there seemed to be a similar etanercept treatment effect in subpopulations defined by having concomitant other inflammatory conditions. Then you look on the safety side to see whether or not potentially a certain extra-skeletal manifestation maybe was worsening, and then sort of from that evolved the question about whether or not one should look specifically at other studies, to design studies, to see whether or not these other manifestations actually may be improved with potentially leading to additional claims.

But I think you answered adequately, but there's sort of different aspects of the extra-skeletal aspects of the disease that one could look at and we're just trying to cover whether or not there's anything more that should be asked for in potentially a post-marketing type of setting.

DR. WILLIAMS: We were discussing at lunch rheumatoid arthritis, that we see less vasculitis and Felty's syndrome and other manifestations that we used to see, and whether that's because the disease has changed or

because we have better treatments, we'd like to think it's because of what we do, but we don't have any good evidence for that, but they certainly have decreased. I would suspect you'll see the same thing with ankylosing spondylitis. However, to prove that will be just as difficult as it was for RA. Probably more so because there are fewer patients available.

Other comments by the committee?

(No response.)

DR. WILLIAMS: To summarize that question, I'd say that we can't think of any.

DR. FRIES: The only proviso is that if in fact you do get this big outcome study going, you could probably put in some observations on these findings.

DR. WILLIAMS: The fourth question will require another vote. Considering the efficacy and safety data presented on etanercept use in this licensed application, is the risk-benefit ratio favorable for use in patients with ankylosing spondylitis?

Before we vote, we'll open it up for discussion by the committee.

Jim?

DR. FRIES: Well, again, I don't know if I'm going to end up being the abstainer, but I think the question needs to be precisely framed. I think that if in

the framework of the rheumatoid arthritis experience with etanercept, that we accept generally that it has a favorable risk-benefit, as voted by tens of thousands of rheumatologists who are using it in that way, then in fact, the answer to this, if it's qualified to active disease, would be yes, it's in the same range that you see in rheumatoid arthritis, as was pointed out, 60 percent improvements and things of that kind. But I am reluctant to generalize that to all patients who meet the New York criteria for ankylosing spondylitis in the country because those weren't the ones who were studied.

DR. WILLIAMS: Further comments? Jennifer?

DR. ANDERSON: I have a somewhat general comment, not really about the risk-benefit ratio in this particular situation, but just about the presentation of safety data in general, and I'm always so frustrated at the way that it's presented without there being any indication of just when during the study different side effects occurred, and then also in long-term data from post-marketing studies and so forth, the side effects are just presented as happening per patient-year.

I think, just as with efficacy data, you often see results that show how quickly an effect was obtained rather than just what proportion had an effect at the end of the study. I think it would be useful and very

informative to see in clinical trials generally the time course of occurrence of side effects and these could be portrayed in survival curves, Kaplan-Meier type survival curves for different types of adverse events with people who drop out or stop the drug because of some other adverse event being censored and so forth. So you could see the time course for different types of events, and I think that would be a very useful thing to do in general.

I thought this was a possible place to throw this comment in.

DR. WILLIAMS: Other comments?

Dr. Fries has suggested we put "active" before ankylosing spondylitis before we vote since that's what was done in the trial and that's what we have data on. Is there any objection to doing that?

Gary?

DR. HOFFMAN: Well, I think that then becomes a contradiction to -- was it point 1 where we decided not to provide that modifying adjective? It was point 1 where we decided to --

DR. WALTON: Dr. Williams?

DR. WILLIAMS: Dr. Walton?

DR. WALTON: If I could clarify a little bit what our goal on this question is? This question is not intended to ask for a vote on exact phrasing of labeling,

rather advice to the agency on your balancing of the safety and benefit findings.

I think that obviously this affects our thinking about moving forward with an approval for an appropriately phrased indication, but on the indication as well as the rest of the labeling, we would certainly be taking all of the advice that we've heard today very much into account. So I would ask that people not feel that the question is exact phrasing but rather how one balances the benefits and the risks.

DR. WILLIAMS: Gary, did you have further comment?

DR. HOFFMAN: No.

DR. WILLIAMS: Wendy?

MS. McBRAIR: Well, the length of the studies were short obviously. So I think for what we see, that the benefit and the risk-benefit ratio is good, but I think we need to look at these medications being given over a longer period of time to be sure that there isn't any risk in anything we don't know about or risk similar to what we've seen with rheumatoid arthritis. So I would want us to continue to identify that issue for a longer period of time.

DR. WILLIAMS: Jim, do you have comments on Dr. Walton's statement?

DR. FRIES: Well, I don't want to beat a dead horse. I accept the explanation which is very helpful, I think, for the clarification. I just hope people understand the point that I have. I've got a lot of essentially asymptomatic, fully-functioning patients with ankylosing spondylitis, and they couldn't be made very much better. So obviously the benefit for them would be pretty small and that risk would be the same magnitude as it is for the people with more active disease. So there clearly would be some people with a legitimate diagnosis of ankylosing spondylitis in whom the risk ratios would not be the kinds we were shown today. So as long as that message is well heard, which I'm sure it is by now, thank you.

DR. WALTON: Yes. The discussions have been very, very helpful for us about how each of you thinks about the data and how each of you thinks about how it applies to the populations of patients that you see in your practice and that's been very, very valuable. But we just don't want you to feel that you are being boxed into voting on exact phrasing on this question.

DR. WILLIAMS: I'd like to comment on Wendy's comment. Etanercept has got a long history now with rheumatoid arthritis of several years, not long in terms of methotrexate or gold, but several years, and the thing that comforts me is that in these short studies, we don't see

anything that was any different than what we saw in other patients that take etanercept. I agree that we always want to keep vigilant, but I think that we've not uncovered any unusual toxicities in this population of patients.

Other comments? Jim?

DR. FRIES: Well, I would just echo and extend that because I think when we compare rheumatoid arthritis with ankylosing spondylitis, the typical patient here is perhaps 10 years younger. The typical patient here is male rather than female. The typical patient is not on corticosteroids, does not have a lot of co-morbidities and is not carrying the magnitude of the inflammatory burden that the patient with rheumatoid arthritis has. So I think that we could, with fair safety, consider the rheumatoid arthritis experience as being at the upper limit of what you might see with ankylosing spondylitis and the likelihood being that you would actually have a more favorable safety experience with ankylosing spondylitis.

DR. WILLIAMS: Further comments?

(No response.)

DR. WILLIAMS: Are we prepared then to take a vote on whether or not the risk-benefit ratio is favorable for the use of patients in ankylosing spondylitis?

Let me read this question. Considering the efficacy and safety data presented on etanercept use in

this license application, is the risk-benefit ratio favorable for the use in patients with ankylosing spondylitis?

Those who would vote yes?

(A show of hands.)

DR. WILLIAMS: That's 6-0.

Question number V. The ASAS Working Group had five domains. Four of the five went into their ASAS 20 response criteria. The fifth domain was spinal mobility. However, in these studies, they did test spinal mobility by clinical testing. The questions are two parts.

Part A. Please discuss the clinical significance of the changes in spinal mobility observed in the studies with etanercept. And B. Please discuss whether agents which improve spinal mobility should be recognized as offering a distinct clinical benefit and, if so, how such benefits would be accurately described in product labeling.

I think those two questions can be taken together. Discussions on those questions?

(No response.)

DR. WILLIAMS: I'll start. I think that the increases in spinal mobility were interesting and of importance. However, I don't know what they totally mean. I think it means that we've treated the disease. We've not

necessarily modified the skeletal manifestations. I think it's worth noting in the label that patients did have improved mobility, but I wouldn't carry that out to a more specific disease modification, similar to what we represent in rheumatoid arthritis.

Others with comments? If you don't volunteer, I'll ask. Frank? Jim?

DR. FRIES: I think, like most of us, we're really glad to see something that's proven hard to move in previous studies start to move a little and that's got to be good. So I think it does have some meaning.

DR. WILLIAMS: Frank?

DR. VASEY: I would agree. I mean, we've heard from the patients and they felt it was very important. I'm not convinced that it adds up to a structural modification. It may be more of a muscle spasm kind of effect, but it's certainly important.

DR. WILLIAMS: Gary?

DR. HOFFMAN: I would probably make a statement that's a little more strongly worded. We know that the course of this disease is one that leads to progressive restriction in movement, and I think it's very heartening to see that over a relatively short period of time, we have some reversal of that loss of movement. To me, that would imply that this is a disease-modifying therapy.

Is it a radiographic-modifying therapy? That, I think, remains to be seen, but I would still urge consideration of the term "disease-modifying" separate from radiographic modifying.

DR. WILLIAMS: Mike, you're the other clinician here. Do you have anything to say?

DR. FINLEY: Well, my thoughts echo what Gary said. As you were reading it, I was thinking about the presentations from our patients earlier this morning and my other patients, and I guess where most clinicians practice and where our patients live, I'm not sure the complete story is understood, and I'm not necessarily sure it's relevant whether it's the pain that we heard about that's diminished. But clearly this notion of moving, as Jim just pointed out, moving something that heretofore didn't move or was progressively getting worse is an important piece that's unique and worth being explicit about perhaps in the label as it's considered.

DR. WILLIAMS: Wendy?

MS. McBRAIR: I like the idea that it's a concrete measurement, and I think sometimes when we hear patients and then we hear scientists, scientists definitely lean towards concrete measurements, and this is one of those and that's kind of exciting to see.

DR. WILLIAMS: I was really impressed with all

the letters that talked about the improvement in function which most of the time was improvement in motion.

Jim?

DR. FRIES: Well, I just remembered that I had a question that I didn't get to this morning, which was the slide that showed that asthenia was actually increased in the etanercept group and yet we did hear the testimonials and certainly the rheumatoid arthritis experience in which a melting away of asthenia is usually the thing.

So what was the thing about those 4 or 5 patients? I mean, what happened? Were they in the subset or what happened with them?

DR. WILLIAMS: This was in one study.

DR. BURGE: The asthenia was not seen as increased in the larger study. There was, as you've noted, an increase in the etanercept group in the smaller study. The reports were basically things like fatigue, but again it's not something that's seen in the larger study.

DR. FRIES: Thank you.

DR. WILLIAMS: Further comments on question V? Dr. Walton?

DR. WALTON: Yes. I'd like to ask to get a little more sense of your thinking. I think much of your discussion has been touching more on the part (B) of the question, and I would like to hear a little bit more about

how we think of the part (A) question, which is, for the measures of spinal mobility that were used in these studies, what size changes on those measures do you think has an observable relevance to a patient where they could tell a difference in their life, whether or not that much change had occurred?

DR. WILLIAMS: Jim?

DR. FRIES: That's the minimal clinically important difference thing, and I think people that have been particularly interested in that question haven't looked at these measures.

I would say from the other things, the effect size on a 5-point scale, which I was seeing that basically the Schober was 1 centimeter better, something on that order of magnitude on a 5-point scale and the average patient had about a 3, so that's really a third of the way, and that would probably meet most of the calculations that I see from minimum clinically important differences.

Now, the correlation between that in that sense, because it's a process measure as has been implicit here, is not really an outcome measure, and your question is what's the relationship of the process measure to the outcome measure, and I don't think we know that.

DR. WILLIAMS: Other comments?

(No response.)

DR. WILLIAMS: I have to agree. I just don't think we've looked at that to consider what would be a minimal meaningful difference, but I have to say that I was impressed and I was just going to look for it. There was one of the slides which showed that most of the measurements in most of the people didn't change very much, but those on Enbrel did change, and I thought the fact that they changed at all was impressive.

I think it's going to take a group of experts to determine what's minimal significant difference.

Jim?

DR. FRIES: Alvin Feinstein used to talk about the miracle of the dancing bear, and it wasn't that it danced well but it was that it danced at all.

DR. WILLIAMS: Frank, you're our local expert. Have you got any comments?

DR. VASEY: I think the patients can probably answer that question the best. I don't have anything to add.

DR. WILLIAMS: We have kind of a slanted view because we only have those that responded, but we don't have all 180 patients to talk to, but those who've responded all felt that they got meaningful changes.

I don't know that we've helped you with that, Dr. Walton.

DR. WALTON: Well, I think you've given us a sense of where your current thinking is, that at the present time, it's hard for you to determine from those measures alone any specific amount of change that can be reliably interpreted as being meaningful to the patient, that that's something that a better understanding of that may develop over time.

DR. WILLIAMS: I think it is fair to say that we were all impressed that they improved at all.

Dr. Weiss?

DR. WEISS: Just along those lines, somebody mentioned the term "disease-modifying", threw that out a little bit earlier, and I'm just curious to know what it takes. I mean, it certainly sounds like something that's more important or ultimately than a signs and symptoms kind of thing. Somebody mentioned -- I think maybe you did, Dr. Fries -- about it would be very helpful if the company followed up with a DMARD kind of claim or outcome, and I guess I'm struggling with how do you do that? What do you look at and for how long and what kinds of things are important to be able to make a claim?

It's done in RA. Everybody talks about DMARDs and throws that term around and maybe they all think they know what it means. It's not really clear, but in particular in AS, how do you go about thinking about that?

DR. WILLIAMS: Well, I think, first of all, the committee is divided on the definition of a DMARD, and I think we're divided on the definition more than on the actual philosophy. Some of us are strict structuralists, saying that there ought to be changes in the musculoskeletal system or a halt in the changes in the musculoskeletal system to say it's disease-modifying. Others say that if you improve the patient functionally, that that would also be disease-modifying, and so I think that our biggest disagreement on the panel is more of a definition of disease-modifying than the actual philosophy of it.

My concern is that if we call it disease-modifying based on function, that it may get confusing because disease modification in rheumatoid arthritis is structural.

Jim, you have comments?

DR. FRIES: I don't think we have to do either/or or decide it today.

Fortunately, there's this very good group in ankylosing spondylitis that is thinking about some of these measures and can undoubtedly think about that kind of question. We might ask Dr. van der Heijde. Is this an area of interest for the group, and could you summarize where you are now?

DR. WILLIAMS: Dr. van der Heijde?

DR. van der HEIJDE: It's definitely an area of interest for the ASAS Working Group. We've presented at EULAR, for example, the natural progression of structural damage in a cohort of patients with ankylosing spondylitis, and we've compared three different measures, how to assess structural damage, and from that survey, we were able to show which method is sensitive to show a difference. It seems to be that you need a minimum of two years' follow-up to be able to show progression in a sufficient proportion of patients, and that information can be used when you're also looking at the progression of structural damage in patients treated with Enbrel, for example.

DR. WILLIAMS: Are you referring to radiographic progression?

DR. van der HEIJDE: Yes.

DR. WILLIAMS: Or are you referring to the clinical signs that you were using?

DR. van der HEIJDE: No. That's really the radiographic progression.

What is also our idea is to look at, for example, the progression of spinal mobility, how that naturally is in a cohort of ankylosing spondylitis and again that can be used to compare the data obtained in 24 weeks as it is here and also during longer follow-up.

DR. WILLIAMS: We often talk about 2 years for OA and 1 year for RA. Ankylosing spondylitis tends to move slowly. Is 2 years adequate?

DR. van der HEIJDE: Yes, it is. It was also to our surprise that 2 years was sufficient. We have data with 1-year follow-up, 2-year and 4-year follow-up of radiographic progression, but clearly 2 years was enough and 1 year not.

DR. FRIES: To frame it on the functional ability side or work disability or some of these other endpoints which in some ways represent slightly softer but more important endpoints, and so that's the same problem we've been having with RA when we met talking about functional limitations, functional activity endpoints for rheumatoid arthritis, and it's a very similar thing here.

I think increasingly we're going to try and get as much length as we can. We need to get as much length as we can in studies, and then we need to use area under the curve analyses, so that you're looking at the extent of benefit over time as well as the absolute amount of benefit at some time of maximum response, and from what I'm hearing and from the testimonials, it sounds as though it's a pretty good likelihood that there will be some long-term effectiveness.

But I think that the changing of the disease

modification in some way has to take some significant fraction of the disease course and represent it, and with a long disease like this, that can be an extended period which is why I was suggesting that we consider some way of combining observational studies with a shorter-term placebo control for them so that we could get maybe some pretty fancy matching on characteristics and be able to get a valid handle on this going forward and be able to answer both the functional limitation question and the radiographic question.

DR. WILLIAMS: I think it may be best to stay away from the term "disease modification" and state that you either improve function or you improve x-rays, and that way, you would describe what you're talking about because I have to agree that if you improve function, you have modified the course of the disease, but since my general expertise is RA, that's not what I think of in RA.

Frank?

DR. VASEY: I would agree. I mean, under that definition, then non-steroidals would be disease-modifying from the standpoint they improve function.

DR. WILLIAMS: Further comments on question V? Did we answer your question, Dr. Weiss?

DR. WEISS: Yes.

DR. WILLIAMS: If I can attempt to summarize

what we decided on this question, the committee feels that the changes in spinal mobility were important and that they were impressive. On the question of whether you consider that disease modification, it would probably be best to describe what happened rather than give it a term. They did have an improvement in their function, including mobility, but there was no evidence presented that we changed radiographic evidence of the disease.

Hearing no objection to that summary, we'll move on to number VI.

DR. WEISS: Can I just ask? The sponsor had mentioned that they didn't have the radiographic data, but are you planning on submitting radiographic findings to us sometime?

DR. WILLIAMS: Dr. Burge?

DR. BURGE: I've been waiting to answer this question.

(Laughter.)

DR. BURGE: The patients from both the 16.0037 primary study that Amgen has had going and the Wyeth study have all had the opportunity to roll into open label extension studies. The studies are for up to 2 years and we got x-rays at baseline in all these patients and plan to get repeat x-rays at 2 years on the patients that are in this cohort. Additionally, we've been evaluating MRs in

patients in the study as well.

DR. WILLIAMS: What will be your control group?

DR. BURGE: Well, we're working on that, but one of the challenges obviously is the lack of a control group, and one of the discussions is using the database, the historical control, from the work that Dr. van der Heijde has discussed.

DR. WILLIAMS: It would be hard based on your data to have a placebo control now.

DR. BURGE: Yes.

DR. WILLIAMS: Question number VI. Ankylosing spondylitis is a lifelong disease associated with significant disability. Please discuss whether further investigation is warranted regarding the long-term effects of etanercept in ankylosing spondylitis, including the types of long-term follow-up, registry, types of comparisons, et cetera, and optimal duration of follow-up.

This is not so much a question as a discussion item. We have discussed a fair amount of this as we've gone along, and we just talked about in terms of radiographic change. I think Dr. Fries' point of a long-term open study with an initial blinded start may be the best approach.

DR. FRIES: I think I was very heartened to hear that the sponsor is doing some things that can fold

into some of this because I really would like to see those data at some time, and I think they will probably be positive data. So it would be kind of nice to see them.

Yes, I think if you're going to start over now, I think you try and put in a short placebo-controlled group and/or, slightly more dangerously, a methotrexate-controlled group. I mean, you could think about prolonging it a little bit by using a drug which has almost predictably some lesser degree of activity against the disease but might allow some compliance.

But I think you're not starting over again. It sounds to me as though you're rolling these three studies forward and you have some people that have been exposed for quite awhile and you have some methods that can be approached to get some progression points, based on better understanding the course of ankylosing spondylitis for the individual patient. The trick is that there obviously are different rates of progression for different patients, and you can get an awful lot of variance in by that.

So you are really, I think, going to have to take for each patient and give a predicted slope or a predicted 3-year outcome or something like that, based on the variables of each patient, recomputed as a goal for that or kind of an expected value for that patient out at whatever length of time you have, and then compare what you

observe with what you previously had put in the drawer as what you expected to see happen over the 3 years.

I think, particularly if you're able to work it out with the FDA into a design which is sort of prespecified as acceptable, even though it won't be perfect, I think you would have a chance to build on what you've already done and get some useful things.

DR. WILLIAMS: I'm assuming that when you're doing this 2-year follow-up on x-rays, you're also obtaining efficacy and safety variables, Dr. Burge?

DR. BURGE: Yes. All the patients are being followed on a very periodic basis for safety and efficacy.

DR. WILLIAMS: Frank?

DR. VASEY: I wondered how critical -- and again, I'm not an epidemiologist. How critical it is that you randomize the patients. I wondered if certain patients are still frightened of TNF blockade understandably. I wondered if those patients could take sulfasalazine or methotrexate or either or both and perhaps they'd be willing to be the control group in one sense in an open-label fashion.

DR. WILLIAMS: Jim?

DR. FRIES: Yes. We do a lot of that kind of study and we like it. It's a usual-care control and you just have to recognize with any quasi-experimental design

that you really have to make sure that you have a very precise protocol and you specify the variables that you wish to adjust for and follow closely, and then you let one guy go with usual care and the other go with etanercept. You could even go the one step further and let people cross over and so forth, but then the analyses get pretty complex.

DR. WILLIAMS: Mike?

DR. FINLEY: I would really be interested in quality of life measures going forward. I'm concerned that if you look only at x-ray data that's planning to be collected 2 years out, there's that window from the time someone starts therapy. The notion in thinking about what we do in rheumatoid arthritis, part of the reason that we either break off therapy or sustain therapy is because we think we have a sense of the natural history of the disease and how soon erosions might or might not appear.

I suspect that, at least for me, there's a certain level of discomfort, and I'm not sure I know that in AS, and so how would you determine in that window as you're waiting for some of these measures that the ASAS Working Group was talking about is that you have a responder and maybe the quality of life measures in the sulfasalazine/methotrexate group early on would be similar to the etanercept group, and then it really gets pretty

muddy.

DR. WILLIAMS: Jim?

DR. FRIES: We could ask the sponsor again to kind of respond as to what you are collecting. I assume that you are probably collecting all of the stuff that you collected in the randomized portion of the trial, so that you would have the Bath Functional Index and you'd have the Bath Disease Activity Scale and all of the other kinds of things and that you would periodically do some mobility measurements and things like that. Is that a correct surmise?

DR. WILLIAMS: Dr. Burge?

DR. BURGE: Yes. We are collecting all the instruments that we had in the original trial. We're additionally looking at SF-36, Euro-QOL, lost work days, hospitalization days, things like that.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I wonder if I could ask Dr. Fries for some clarification. You said that you'd like to get some prediction about the expected outcome for patients presumably based on their baseline variables. Can you be more specific about what you mean? Do you mean with respect to x-ray in terms of how active the patient is or of their baseline x-rays?

DR. FRIES: Well, I speak as an outside to this

area. So we have one genuine expert for sure, maybe some other people. I was just talking in general in terms of the designs and the way that you would go. And in a variable way, if you're trying to compute an expected value at some future point in time and predict that, then you need to know what the variables are that affect the slope of progression of whatever dependent variables you have.

My understanding is that the historical controls that the group is working with would allow them to do that and generally rather than try and predict a mean for the entire group, based on adjusting for their characteristics, it's generally a little bit better to match them in such a way that you're actually making the prediction with your model for each individual person and then it represents the mean on the observed side and the mean on the expected side and you're comparing those.

So the general principle would be the kinds of variables I would test would be the severity of all of the markers at baseline. I'd probably test a variable made up of a duration plus a finding, so that you were able to get a rate, so you would try and extrapolate back to when the disease began which is not always obvious in ankylosing spondylitis, but you would attempt to get a slope which was related to the duration of the illness and then the magnitude at a particular slot, and then you would just try

these against your historical data and see what gave you the best predictive model, probably doing a stepwise multiple regression of some type, and then whatever fitted into that model, use that to make the predictions on the individual. So that's the process I would go through.

Now, the people that worked here have a much better feel for how these variables behave, the specific variables behave in ankylosing spondylitis, but sometimes it's sort of empiric to put your models together.

DR. WILLIAMS: Jennifer?

DR. ANDERSON: I'd just like to make a comment about this type of study, registry or other long-term follow-up. It's very important, I think, that the patients stay in the registry, even if they stop taking Enbrel. If patients just sort of drop off the face of the earth, they're just completely lost to follow-up if they stop taking the drug, that's not very useful data, and so patients should just be kept in just as if they were still taking the drug.

DR. WILLIAMS: Further comments? Jim?

DR. FRIES: Well, after some period of time, you're going to end up having to do an intention-to-treat analysis and a completers' analysis because no matter what you'll do, they'll drop off. But I really take your point and would hope that during this standard, people are

getting free Enbrel or there are some reasons for them to maintain in the study because interpretability will depend upon the percentage of people and the rate of dropouts.

DR. WILLIAMS: Further comments? Further questions from the FDA? Dr. Weiss?

DR. WEISS: Just one more question, a follow-up I think to Dr. Fries also. You expressed some concern about this product being used perhaps in people who are relatively asymptomatic. I also heard a lot of comments that there's an inexorable progression of eventually more spinal mobility issues and problems over time, though that rate probably varies quite a bit, but it tends to be a known sort of end result, if I'm hearing the discussions correctly.

I mean, I could just understand that patients who would be relatively newly diagnosed who don't have some -- it's the whole issue, I guess, of active disease or moderate to severe, whatever you call it, where you had some concerns, and whether or not you had any thoughts about if relatively newly-diagnosed or relatively-asymptomatic people were interested in using this with the idea that it might delay ultimately accumulation of problems, how best that could be evaluated. I think it's, to some extent, maybe the issue of trying to evaluate people earlier on in their disease and looking at whether

or not something can actually slow down the accumulation of a disability.

We had lots of discussions a number of years ago with RA and the "prevention" word. I don't know if anybody was at the committee at that time, but a lot of concern about using that particular word, feeling more that something that -- more likely the products would delay or slow down or whatever. But those are just questions which would perhaps best be addressed in some kind of controlled trial, perhaps looking at people with somewhat earlier manifestations of the disease, and is there some way that that could be evaluated?

DR. FRIES: Well, I'll just give my feeling and then some other clinicians that have seen a lot of AS can also kind of indicate it.

It's different from RA. In RA, there's some place between 5 or 10 percent of most series of people that are carrying a diagnosis that essentially do just great over a long period of time and never become disabled. The blood donor studies would suggest in AS that there are a reasonable number of people who would really be better called symptomatic sacroiliitis, and their disease never really grows any further than the sacroiliac joints which actually you can do without much wiggle room in, and they function well normally. Many of those patients don't even

take NSAIDs on a regular basis. And then there's another group above that in whom NSAIDs are really quite effective, and they may be quite effective for portions of the course or for all of the course. And then you get into people who are just the -- I don't want to use a slang term, but they just have very, very difficult disease to control and it's clear for them this kind of a tool and probably for people that are even partway there, it's going to be a very, very powerful thing for them.

So my concern is just that if I take the guy that works opposite me in my Thursday afternoon clinic for the last 30 years who has ankylosing spondylitis and has never taken anything for it, has never had any kind of problem, he's got New York criteria ankylosing spondylitis, but it's confined to the sacroiliac joint. He has normal mobility and so forth. He's had the disease for 40 years. So there are a lot of people that are in that mild area.

I think if we learned the lesson from rheumatoid arthritis about disease modification, it's really that we tend to slow the development of structural problems and functional problems in the hands. It's not that we keep it entirely over a long enough period of time. There still will be advancement, and if someone is on a rapid trajectory, it becomes more important to get them down toward a no evidence of disease area. And I would

guess that that's where we would be heading with ankylosing spondylitis. As was indicated, I think, by the sponsor earlier on, that bar may be being changed, and we may want to get people to a closer area of no evidence of disease than we previously did.

I would like us to find that level sort of gradually by testing it, but I think it is likely that that's where we're going to be and that we'll be seeing a real improvement in our approach to ankylosing spondylitis as a result of having these drugs available. So I think that you do have the opportunity to kind of permanently subtract or if you've got a given slope which represents the severity of that disease in an individual and if you move that back down and postpone it three years, there will be less lifetime problem. If you postponed it all the rest of the time, you might get rid of almost all of it.

So there's not exactly a glib answer. It's a complex mechanism.

DR. WILLIAMS: Fred?

DR. LASKY: As a nonclinician, if I can add to that in terms of what is not clear to me, is how this would be provided for the patient in terms of whether or not we're dealing with an inflammatory process where it's given on a flare-up basis and then reduced or eliminated and monitored and then the patient monitored and then put back

on the drug. Based on what I've heard today, it appears obvious that there's a lot of benefit in the shorter term, but what happens if patients who have withdrawn from the drug, should they be withdrawn from the drug, and then how is the follow-up, and then how do we monitor that and understand better how this drug is used? Because I think there are two possibilities -- well, there are many, but two that come to mind is -- one is toxicity over long-term use and the other is greater loss of effectiveness as the patients might become immunized to the drug itself.

DR. WILLIAMS: Frank?

DR. VASEY: I don't have too much experience with intermittent use of the drug. I have a few patients that have actually reduced it to once a week and still got a satisfactory result. So we've tended to continue the drug basically. So I really can't answer the question beyond that.

I did want to raise one of the group of patients in follow-up to what Jim said, and those are the patients that you encounter occasionally in the hospital or for some other reason, they have a fused spine and they deny any symptoms. That's always very perplexing. You don't know if they have a high pain threshold or what the problem is, but somehow they fuse their spine and didn't notice. So again a radiographic study would probably pick

some of those people up perhaps, if they would even get in it. I guess they probably wouldn't. But the amount of symptoms people have do vary.

DR. WILLIAMS: Further comments? Further questions from the FDA?

(No response.)

DR. WILLIAMS: I would like to thank the members of the committee for being very open in their discussion and for being prepared and for all that you've done taking your time to be here.

We will stand adjourned.

DR. WEISS: Thank you very much, Jim.

(Whereupon, at 1:45 p.m., the committee was adjourned.)