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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
ARTHRITIS ADVISORY COMMITTEE

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Wednesday,  
September 16, 1998

Ballroom  
Holiday Inn Gaithersburg  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

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Division of Clinical Trial Design & Analysis 93

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P R O C E E D I N G S

(8:05 a.m.)

1  
2 DR. PETRI: Ladies and gentlemen, my name is  
3 Michelle Petri, and I want to welcome all of you to the  
4 Arthritis Advisory Committee meeting today. Our subject  
5 today will be Enbrel, for the treatment of rheumatoid  
6 arthritis.

7 I'd like to start by asking everyone at the  
8 front table to introduce themselves. If you're not a  
9 member of the Arthritis Advisory Committee, could you  
10 please state your role here today, and I'll start at my  
11 left.

12 Dr. Silverman?

13 DR. SILVERMAN: I'm Earl Silverman. I'm a  
14 special guest to the advisory committee, pediatric  
15 rheumatologist, Hospital for Sick Children in Toronto.

16 DR. KATONA: I'm Ildy Katona. I'm from the  
17 Uniformed Services University. I'm also a pediatric  
18 rheumatologist, member of the arthritis panel, and I'm also  
19 the chairman of pediatrics at the Uniformed Services  
20 University.

21 DR. GOLDSBY: I'm Dick Goldsby from Amherst  
22 College. I'm a guest of the panel, and I'm visiting from  
23 the Biological Response Modifiers Committee.

24 MS. MALONE: I'm Leona Malone. I'm the  
25 consumer rep on the committee.

1 DR. HARRIS: I'm Nigel Harris. I'm on the  
2 Arthritis Committee. I'm dean at Morehouse School of  
3 Medicine and a rheumatologist.

4 DR. FRIERI: I'm Marianne Frieri, director of  
5 allergy and immunology at Nassau County Medical Center, and  
6 associate professor of medicine and path at the State  
7 University of New York at Stony Brook.

8 DR. YOCUM: Dave Yocum, part of the advisory  
9 panel, University of Arizona, section of rheumatology.

10 DR. SIMON: I'm Lee Simon. I'm a member of the  
11 advisory committee, and I'm at the Beth Israel Deaconess  
12 Medical Center in Harvard Medical School.

13 DR. LUTHRA: I'm Harvey Luthra. I'm a  
14 rheumatologist at the Mayo Clinic and a member of the  
15 advisory committee.

16 DR. LIANG: Matthew Liang, rheumatologist at  
17 the Brigham and Women's Hospital in Boston, and a member of  
18 the advisory committee.

19 DR. TILLEY: Barbara Tilley, biostatistician at  
20 Henry Ford Health System in Detroit, and I'm a member of  
21 the advisory committee.

22 DR. FREAS: I am Bill Freas. I am the acting  
23 executive secretary for the day. For those of you who are  
24 wondering, the normal executive secretary of this  
25 committee, Kathleen Reedy, is doing research in Antarctica,

1 but she will be back for your next meeting, we hope.

2 (Laughter.)

3 DR. ABRAMSON: Steve Abramson, rheumatologist  
4 at the Hospital for Joint Diseases, NYU.

5 DR. CALLAHAN: I'm Leigh Callahan, an  
6 epidemiologist at the University of North Carolina in  
7 Chapel Hill, and an FDA consultant advisory committee  
8 member.

9 DR. HESS: I'm Evelyn Hess from the University  
10 of Cincinnati Medical School, and I'm here as a CBER  
11 consultant.

12 DR. BRANDT: Ken Brandt. I'm a rheumatologist  
13 from the Indiana University School of Medicine, and I'm a  
14 consultant to the advisory committee.

15 DR. PUCINO: Frank Pucino, National Institutes  
16 of Health. I'm a pharmacist, and I'm with the advisory  
17 committee.

18 DR. FELSON: David Felson, rheumatologist from  
19 Boston University, and I'm here as an FDA consultant.

20 DR. JEFF SIEGEL: Dr. Jeffrey Siegel, Center  
21 for Biologics at the FDA. I'm a clinical reviewer on  
22 Enbrel.

23 DR. WEISS: Karen Weiss at the Center for  
24 Biologics, FDA.

25 DR. JAY SIEGEL: Jay Siegel, Center for

1       Biologics, FDA.

2                     DR. PETRI: Thank you.

3                     I'm now going to turn the meeting over to Bill  
4       Freas, who will give us our meeting statement.

5                     Bill?

6                     DR. FREAS: Good morning. I'm going to read  
7       the following conflict of interest statement into the  
8       public record:

9                     "The following announcement addresses the issue  
10       of conflict of interest with regard to this meeting and is  
11       made part of the record to preclude even the appearance of  
12       such at this meeting.

13                    "Based on the submitted agenda for the meeting  
14       and all financial interests reported by committee  
15       participants, it has been determined that all interests in  
16       firms regulated by the Center for Drugs Evaluation and  
17       Research and by the Center for Biologics Evaluation and  
18       Research present no potential for an appearance of a  
19       conflict of interest at this meeting, with the following  
20       exceptions:

21                    "In accordance with 18 USC 208(b)(3), full  
22       waivers have been granted to Dr. Steven Abramson, Dr.  
23       Matthew Liang, Dr. Frank Pucino, Dr. Lee Simon, Dr. David  
24       Yocum, Dr. Kenneth Brandt, Dr. Leigh Callahan, Dr. David  
25       Felson, Dr. Félix Fernandez-Madrid, and Dr. Marianne

1 Frieri. These waivers permit participants to participate  
2 in discussions on the matters concerning Enbrel. A copy of  
3 the waiver statement may be obtained by submitting a  
4 written request to the agency's Freedom of Information  
5 Office, Room 12A-30 of the Parklawn Building.

6 "FDA's invited guest speaker, Dr. Earl  
7 Silverman, has reported an interest that we believe should  
8 be disclosed to the public in order for you to objectively  
9 evaluate his comments. Dr. Silverman reported that he is a  
10 co-investigator on an Enbrel study in juvenile rheumatoid  
11 arthritis. As a guest, he will not be voting with the  
12 committee.

13 "In the event that the discussions involve any  
14 products or firms not on the agenda, for which an FDA  
15 participant has a financial interest, the participants are  
16 aware of the need to exclude themselves from such  
17 involvement, and their exclusion will be noted for the  
18 record. With respect to all other participants, we ask in  
19 the interest of fairness that they address any current or  
20 previous financial involvement with any firm whose products  
21 they may wish to comment upon.

22 "In addition, the director for the Center for  
23 Drugs Evaluation and Research has appointed Dr. Kenneth  
24 Brandt, Dr. David Felson, Dr. Barbara White, Dr. Leigh  
25 Callahan, and Dr. Ildy Katona as temporary voting members

1 for today's discussion. The director for the Center for  
2 Biologics Evaluation and Research has appointed Dr.  
3 Marianne Frieri, Dr. Richard Goldsby, and Dr. Evelyn Hess  
4 as temporary voting members for today's discussion as  
5 well."

6 So ends the reading of the statement for the  
7 public record.

8 DR. PETRI: Thank you.

9 Dr. Kathleen Clouse, senior investigator for  
10 the Division of Cytokine Biology, Office of Therapeutics  
11 Research and Review, will now give some opening remarks.

12 DR. CLOUSE: I'm Dr. Kathleen Clouse. I'm  
13 chairman of the Biologic License Application Review  
14 Committee. I'm also the primary product reviewer, and I  
15 would like to acknowledge the members of the BLA Review  
16 Committee for their contributions to this review. Then I  
17 would like to briefly review the biology of tumor necrosis  
18 factor receptors prior to introducing the product under  
19 review. I will be followed by Dr. Ken Seamon from Immunex  
20 Corporation, who will give additional information regarding  
21 the product.

22 As I mentioned, I am one of the product  
23 reviewers for this license application. The other product  
24 reviewers are John Hill and Kurt Brorson. Dan Kearns is  
25 the facility reviewer. Dr. Jeffrey Siegel, who will

1 present later, is the clinical reviewer for this product.  
2 Vance Berger is the statistician. Dave Green, who will  
3 also speak later, is the pharmacology/toxicology reviewer.  
4 Lisa Rider is the pediatric reviewer. Mary Andrich was  
5 responsible for the bioresearch monitoring, and Earl Dye is  
6 the regulatory coordinator for this application.

7 Tumor necrosis factor receptors exist as two  
8 types. They're classified as Type 1 or Type 2, which  
9 corresponds to a 55-kilodalton or a 75-kilodalton receptor.  
10 They're both Type 1 membrane proteins, and the sequence  
11 homology for these two proteins is limited to the  
12 extracellular portion of the molecules, as shown here. The  
13 sequence homology enables both receptors to bind tumor  
14 necrosis factor, and they bind it with equal affinity, but  
15 the off-rate of the molecule once it's found differs  
16 somewhat. The function and the signal transduction  
17 pathways are distinct for these two receptors, and that is  
18 determined by the cytoplasmic portions of both molecules.

19 Now, these receptors exist in membrane form and  
20 also in soluble form. The soluble receptors are generated  
21 by cleavage of the extracellular portion of the membrane,  
22 and they exist under normal physiologic conditions.  
23 Similar to the tumor necrosis factor receptors, both  
24 soluble and membrane forms of tumor necrosis factor exist,  
25 and as shown in this slide, although it's not very clear in

1 this slide, the biologically active form of tumor necrosis  
2 factor is a homotrimer, and it generally binds to three  
3 receptor molecules expressed on the cell surface, and it  
4 can bind, as I mentioned, to both the p55 and p75  
5 receptors, and the biological response is then determined  
6 by the cytoplasmic regions of the receptors.

7 Now, soluble TNF receptors can modulate this  
8 binding or interfere with this binding for both the soluble  
9 TNF and the membrane form of the receptor. Because the  
10 biologically active form of tumor necrosis factor is a  
11 homotrimer, blocking this interaction with membrane TNF  
12 receptors using a monomeric form of receptor is not very  
13 efficient, which sets the stage for the rationale for  
14 developing multimeric soluble receptors if you want to  
15 inhibit this reactivity.

16 Using this approach, Immunex Corporation has  
17 generated the following product. The USAN designation for  
18 this is etanercept. The proposed trade name is Enbrel.  
19 This product was generated using the extracellular portion  
20 of the p75 TNF receptor, and this extracellular portion was  
21 fused to the Fc portion of human IgG1. This resulted in  
22 the generation of a dimeric soluble receptor, and it's  
23 referred to as the p75 TNF receptor:Fc fusion protein. The  
24 binding constant for this is  $10^{10}$ , which is equivalent to  
25 membrane-expressed TNF receptors.

1                   This product is produced in mammalian cell  
2 culture, and it followed the transfection of a mammalian  
3 cell with a construct containing the human p75 TNF receptor  
4 gene, which is linked to the human IgG1 Fc region gene.  
5 The mechanism of action for this molecule for rheumatoid  
6 arthritis is dependent on the TNF receptor portion of this  
7 molecule.

8                   Now, regarding the manufacturing of this  
9 product, the commercial process for Enbrel production has  
10 been expanded eight-fold since the pivotal clinical trials.  
11 Several manufacturing issues remain, but CBER is working  
12 directly with the company to resolve the issues.

13                   DR. PETRI: Thank you.

14                   We're now going to turn to the Immunex  
15 presentation, and I'd like to introduce Dr. Kenneth Seamon,  
16 who's the senior vice president for drug development at  
17 Immunex.

18                   Dr. Seamon?

19                   DR. SEAMON: Good morning, members of the  
20 advisory committee, officials of the Food and Drug  
21 Administration, and participants from the general public.  
22 Immunex is here today to present data which demonstrates  
23 that a soluble human TNF receptor called Enbrel can produce  
24 significant clinical benefit for patients with active  
25 rheumatoid arthritis. This data will support the use of

1 Enbrel for treating the signs and symptoms of the disease.  
2 Enbrel significantly decreases disease activity, increases  
3 functional ability, and improves quality of life. In  
4 addition, we will show data that demonstrates that Enbrel  
5 is effective alone or in combination with methotrexate.

6 Enbrel is a recombinant fusion protein  
7 consisting of two extracellular domains of the p75 TNF  
8 receptor linked to the Fc region of human IgG1. Enbrel  
9 consists entirely of human amino acid sequences. Enbrel is  
10 the trade name for the product, and etanercept is the USAN  
11 name. Enbrel has also been referred to as TNF receptor;  
12 however, for the purpose of today's discussion, we will be  
13 referring to this as Enbrel.

14 Immunex will give three presentations. I will  
15 give a brief introduction and summary, Dr. Leslie Garrison  
16 will provide the clinical safety and efficacy data, and Dr.  
17 Ann Hayes will conclude with an overall summary and will  
18 mediate questions.

19 We have four consultants present today, who are  
20 lead investigators and participated in the design of our  
21 clinical program: Dr. Edward Giannini of Children's  
22 Hospital Medical Center in Seattle, Dr. Larry Moreland of  
23 the University of Alabama in Birmingham, Dr. Harold Paulus  
24 of the University of California at Los Angeles, and Dr.  
25 Michael Weinblatt of Brigham and Women's Hospital in

1 Boston. In addition, we have other Immunex staff,  
2 colleagues from our development partner, Wyeth-Ayerst, and  
3 other consultants to provide additional information on  
4 specific questions.

5 I will now provide a brief summary into the  
6 scientific rationale for Enbrel as a specific inhibitor of  
7 TNF in rheumatoid arthritis, the mechanism of action of  
8 Enbrel, the preclinical studies and our clinical program,  
9 and FDA interactions.

10 Rheumatoid arthritis is a chronic, progressive  
11 disease that results in significant morbidity and mortality  
12 for over 2 million patients. Over 50 percent of patients  
13 experience substantial functional loss within 5 years of  
14 disease onset, and life expectancy is decreased an average  
15 of 4 to 10 years as compared to the general population.

16 Current therapies are directed at controlling  
17 and limiting the inflammatory process through a variety of  
18 pathways. These include inhibitors of prostaglandin  
19 synthesis, such as non-steroidal anti-inflammatory drugs,  
20 immune suppressive agents, antimetabolites such as  
21 methotrexate, and other drugs that control disease symptoms  
22 through a variety of mechanisms that are relatively  
23 defined. Many patients become unresponsive or are  
24 intolerant of current therapies over time. In addition,  
25 many of the current therapies also have broad effects,

1 since they were not initially developed for rheumatoid  
 2 arthritis and do not specifically target the inflammatory  
 3 process. There is a need for additional antirheumatic  
 4 therapies that are well tolerated and can affect the  
 5 disease process through specific targeted mechanisms.

6 TNF is a cytokine which is produced primarily  
 7 by macrophages and T-cells and is produced locally in the  
 8 synovium and cartilage pannus junction. TNF is one of the  
 9 body's major biological mediators of inflammation and is  
 10 responsible for initiating specific events in rheumatoid  
 11 arthritis. TNF induces the activation of matrix-degrading  
 12 enzymes, leading to bone and cartilage resorption; it  
 13 increases adhesion molecules, leading to increased cell  
 14 migration into joints; and TNF also induces other  
 15 proinflammatory cytokines, such as IL-1 and IL-6, leading  
 16 to increased inflammation.

17 TNF is, therefore, thought to occupy a dominant  
 18 position in the inflammatory cascade. This inflammatory  
 19 cascade is responsible for the disease symptoms and joint  
 20 damage associated with rheumatoid arthritis. Therefore,  
 21 inhibition of TNF biological activity by Enbrel represents  
 22 a targeted therapy to block inflammation associated with  
 23 rheumatoid arthritis.

24 There are several approaches for inhibiting TNF  
 25 biological activity. Small molecules could be used to

1 interfere with TNF signaling, to inhibit TNF production or  
2 act as receptor antagonists. Alternatively, monoclonal  
3 antibodies against TNF could also be used as TNF  
4 antagonists. Immunex has developed an approach of using  
5 naturally occurring soluble TNF receptors for inhibition of  
6 TNF biological activity to provide a targeted therapy for  
7 inflammation in rheumatoid arthritis.

8 The different approaches for inhibition of TNF  
9 biological activity each have unique mechanisms of action  
10 and patient exposures due to different dosing schedules and  
11 pharmacokinetic characteristics. Therefore, it is  
12 difficult to generalize among anti-TNF therapies, and it is  
13 important to evaluate the safety and efficacy of each  
14 product with respect to its own clinical data.

15 There is very good rationale for the use of  
16 soluble TNF receptors for inhibiting the TNF-mediated  
17 inflammatory process in rheumatoid arthritis. Soluble TNF  
18 receptors occur naturally. They are thought to actually be  
19 involved in regulating the activity of TNF and are elevated  
20 during inflammatory processes. Soluble receptors bind to  
21 TNF with high affinity and specificity and compete with the  
22 binding of TNF to the cell membrane-bound receptors and  
23 are, thus, very effective antagonists. In addition,  
24 soluble receptors provide a safe approach for inhibiting  
25 the inflammatory process. They are relatively non-

1 immunogenic, since they are based entirely on human amino  
2 acid sequences, based on naturally occurring molecules. In  
3 addition, they have no intrinsic pharmacological activity  
4 and act only by inhibiting the biological activity of TNF.  
5 Therefore, soluble TNF receptors represent a good approach  
6 for developing a therapeutic drug with minimal potential  
7 for adverse events.

8 This slide depicts the interaction of TNF with  
9 cell surface TNF receptors and Enbrel, as previously  
10 described by Dr. Clouse. TNF exists primarily as a  
11 homotrimer, and its biological activity is dependent upon  
12 cross-linking of two cell surface membrane receptors to  
13 initiate an intracellular signal. TNF, which is bound by  
14 Enbrel, is not able to bind to the cell surface receptors  
15 and is, therefore, biologically unavailable and inactive.  
16 The mechanism of action of Enbrel is, therefore, through  
17 the competitive inhibition of the binding of TNF to the  
18 cell surface receptor.

19 Because of the need for a multivalent  
20 interaction of TNF at the membrane receptor, Enbrel was  
21 developed to contain two TNF binding sites by fusing two of  
22 the extracellular binding domains of the human p75 receptor  
23 to the Fc region of IgG1. Enbrel binds TNF with affinity  
24 of approximately  $10^{10}$ , which is comparable to the affinity  
25 of cell surface receptors. TNF which is bound to Enbrel is

1 unable to bind to cell surface receptors, making Enbrel a  
2 very effective antagonist.

3           Although Enbrel contains the Fc region of IgG1,  
4 it does not fix complemented solution either in the  
5 presence or absence of TNF and does not lyse cells  
6 expressing membrane TNF in the presence of complement.  
7 Therefore, Enbrel does not lead to killing of TNF-producing  
8 cells. Thus, the major biological activity of Enbrel is  
9 due to the binding of TNF, resulting in decreased levels of  
10 biologically active TNF.

11           Enbrel is effective in various preclinical  
12 models of arthritis. Enbrel is effective in treating  
13 antigen-induced arthritis in rats, as well as arthritis in  
14 TNF transgenic mice. Enbrel is also effective in the  
15 standard collagen-induced arthritis model, in which mice  
16 develop inflammation and tissue degradation in response to  
17 the administration of heterologous collagen. In this  
18 model, Enbrel led to a reduction in the incidence of joint  
19 inflammation and tissue degradation, as well as decreased  
20 joint damage. The effects were dose dependent, and Enbrel  
21 was effective when given in a preventative protocol prior  
22 to disease onset, as well as therapeutically when given  
23 after disease onset.

24           This slide shows the effects of Enbrel on joint  
25 pathology in the CIA model in mice. The left-most bars

1 indicate the beneficial effect of Enbrel on clinical  
2 arthritis score, as determined by joint swelling; the  
3 center bars indicate the beneficial effect of Enbrel on  
4 joint structure, as defined histopathologically; and the  
5 right-most bars indicate the beneficial effects of Enbrel  
6 on joint structure, as defined by a reduction in cartilage  
7 depletion. In each case, Enbrel led to significantly less  
8 joint damage than control.

9           Enbrel was well tolerated in all species used  
10 in preclinical toxicology studies. Enbrel was well  
11 tolerated with no significant adverse events in acute and  
12 chronic studies in non-human primates. In addition, Enbrel  
13 did not produce any maternal or developmental toxicity in  
14 reproductive toxicity studies in rats or rabbits. Also,  
15 Enbrel did not demonstrate any genotoxic effects.  
16 Therefore, Enbrel has shown no pharmacologically adverse  
17 events in toxicology studies, consistent with its mode of  
18 action being only directed at modulating biologically  
19 active TNF levels.

20           The pharmacokinetic parameters of Enbrel were  
21 determined both from individual studies and from population  
22 PK analysis. Enbrel is slowly absorbed from the site of  
23 subcutaneous injection, with a time to peak serum  
24 concentration of 49 hours. The peak serum concentration  
25 after a single 25-milligram subcutaneous dose is 1.64

1 micrograms per mL. A twice weekly dosing regimen was  
2 selected based on the 70-hour elimination half-life of  
3 Enbrel and the desire to maintain a consistent  
4 concentration and provide for convenient patient dosing.

5 The consistency of this dosing schedule was  
6 verified by determining the serum concentrations of Enbrel  
7 in patients in long-term treatment trials. Comparable  
8 levels of Enbrel were observed for patients who were given  
9 twice weekly dosing of Enbrel for 6 months when compared to  
10 patients given Enbrel twice weekly for shorter periods of  
11 time. There is no evidence of either increased clearance  
12 or unexpected accumulation of Enbrel after 6 months of  
13 dosing based on the observed serum concentrations.

14 A total of 1,039 patients with active  
15 rheumatoid arthritis have received Enbrel and are included  
16 in today's review. The data to be presented by Dr.  
17 Garrison will be from three blinded, placebo-controlled,  
18 randomized trials, two with Enbrel alone, plus a  
19 combination study with methotrexate. Several open-label  
20 trials are also included in today's presentation. These  
21 data will demonstrate the consistency of the initial  
22 clinical response to Enbrel in all of these studies, the  
23 duration of this response with continued therapy in this  
24 patient population, and the lack of clinically significant  
25 adverse events.

1           We are here to discuss with you these data to  
2 support the use of Enbrel in patients with active  
3 rheumatoid arthritis who are in need of therapy  
4 alternatives today. However, we also have an ongoing  
5 commitment to continued development of Enbrel in rheumatoid  
6 arthritis. A trial in juvenile rheumatoid arthritis has  
7 completed accrual. Data from the initial open-label  
8 portion of this trial are also included in today's  
9 presentation. The blinded efficacy portion of the study is  
10 currently under analysis. A blinded randomized trial in  
11 early methotrexate-naive patients with active rheumatoid  
12 arthritis is also ongoing. This study will compare  
13 methotrexate and Enbrel and will evaluate by radiographic  
14 studies whether Enbrel modifies the course of joint damage  
15 in rheumatoid arthritis. Both the juvenile rheumatoid  
16 arthritis and the early rheumatoid arthritis studies will  
17 form the basis for supplemental BLA filings.

18           There has been active discussion with the FDA  
19 regarding the design of our program for the development of  
20 Enbrel in rheumatoid arthritis. It was agreed that a  
21 filing would be acceptable based on two randomized,  
22 placebo-controlled studies for active rheumatoid arthritis,  
23 based on the robustness of the data and the lack of any  
24 significant safety concerns. Safety and efficacy in  
25 combination with methotrexate would be provided, as well as

1 additional safety data in juvenile rheumatoid arthritis  
2 patients. The size of our safety database is consistent  
3 with the ICH guidelines on the extent of population  
4 exposure required to assess clinical safety for drugs.

5 FDA designated Enbrel a fast-track drug with  
6 priority review status based on its significant promise for  
7 addressing an unmet medical need for a serious or life-  
8 threatening condition.

9 Enbrel represents a new approach for a safe and  
10 targeted therapy for treating patients with active  
11 rheumatoid arthritis.

12 Dr. Leslie Garrison will now present the safety  
13 and efficacy data.

14 DR. GARRISON: Thank you, Ken.

15 This morning I will review the clinical  
16 experience with Enbrel in rheumatoid arthritis. I will  
17 first discuss efficacy, and then move on to safety. I will  
18 focus on the placebo-controlled, randomized trials shown on  
19 the left side of this slide and demonstrate how data from  
20 open-label and long-term treatment trials support these  
21 results.

22 A variety of enclaves were analyzed to assess  
23 efficacy. The ACR response was assessed, as well as a  
24 number of other parameters: the number of tender and  
25 swollen joints, pain as assessed by a visual analog scale,

1 global assessment of disease status by both physician and  
2 patient, and duration of morning stiffness. Specific  
3 objective laboratory markers of inflammation were also  
4 collected and analyzed, including the erythrocyte  
5 sedimentation rate and the C-reactive protein. To assess  
6 physical function and health-related quality of life, two  
7 questionnaires were administered, the HAQ as well as the  
8 SF-36.

9           The primary endpoint in most of the trials was  
10 the ACR response rate, which is a composite index used to  
11 describe disease activity. The definition of the ACR  
12 response is a 20 percent or greater improvement in the  
13 tender joint count, a 20 percent or greater improvement in  
14 the swollen joint count, and a 20 percent or greater  
15 improvement in three of the following five parameters:  
16 pain, physician global assessment, patient global  
17 assessment, disability, ESR or CRP. Because we wanted to  
18 quantitate improvements of greater magnitude, we  
19 extrapolated from this definition to calculate the 50  
20 percent as well as 70 percent ACR responses.

21           The first placebo-controlled, double-blind,  
22 randomized trial that was conducted was Protocol 16.0004.  
23 This study was a 3-month trial in which patients received  
24 either placebo or one of three doses of Enbrel, 0.25, 2, or  
25 16 mg/m<sup>2</sup>. Study drug was administered subcutaneously twice

1 weekly for 3 months, and 180 patients were enrolled at 11  
2 sites. In this study, we were able to observe the duration  
3 of clinical responses of the patients once Enbrel treatment  
4 was discontinued. In all of our other studies, patients  
5 continued on long-term treatment trials once their original  
6 study was complete.

7 The inclusion criteria are shown here.

8 Patients must have had an inadequate response to at least  
9 one DMARD and have active RA at screening. Patients had to  
10 have at least 10 swollen joints and 12 tender joints. They  
11 also had either an elevated ESR, an elevated CRP, or a  
12 morning stiffness of 45 minutes or more. Patients were  
13 allowed to be on stable prednisone at doses of 10  
14 milligrams a day or less and/or stable NSAIDs throughout  
15 the study, but could not be on DMARDs. If they were on a  
16 DMARD at screening, all DMARDs were discontinued for 4  
17 weeks prior to study drug administration.

18 The primary endpoint in this trial was the  
19 improvement in the number of tender and swollen joints. A  
20 number of other endpoints were also defined, including all  
21 of the individual components of the ACR response criteria,  
22 allowing calculation of the ACR response rate. For joint  
23 counts a last-value-carried-forward approach was utilized,  
24 and for ACR responses an intent-to-treat analysis was  
25 performed.

1           The treatment groups were well balanced. The  
2 average patient in the study was a woman in her mid-50s who  
3 had been diagnosed with rheumatoid arthritis more than 5  
4 years ago. The majority of patients were on concomitant  
5 steroids and NSAIDs at screening.

6           Patients in the placebo group and those  
7 receiving the lowest dose of Enbrel, 0.25 mg/m<sup>2</sup>, had the  
8 lowest rate of study completion. Those receiving the  
9 highest dose of Enbrel, 16 mg/m<sup>2</sup>, had the highest study  
10 completion rate, with 93 percent completing the full 3  
11 months of treatment. Most of the discontinuations were due  
12 to lack of efficacy. Other reasons for discontinuation  
13 were similarly distributed among the groups.

14           The 20 percent ACR response rate is shown here.  
15 On the left is the ACR response rate after 1 month of  
16 therapy, and the right panel shows the ACR response rate  
17 after 3 months of therapy, at the end of the trial.  
18 Significantly more patients treated with Enbrel achieved a  
19 20 percent ACR response than patients treated with placebo.  
20 These responses were rapid, and many patients had a  
21 response within the first month of treatment. For example,  
22 as shown here, in the 16 mg/m<sup>2</sup> dose, 59 percent of patients  
23 achieved the 20 percent ACR response by the end of the  
24 first month of treatment, and 75 percent of patients  
25 achieved the 20 percent ACR response by 3 months. A very

1 clear dose response is seen, with the highest responses  
2 seen with the highest dose tested.

3 To determine how many patients experienced more  
4 substantial improvement, we calculated the 50 percent ACR  
5 response. Rapid responses were seen even at this higher  
6 level of response, with 25 percent of patients achieving a  
7 50 percent ACR response by 1 month of treatment. By 3  
8 months, 57 percent of patients at the 16 mg/m<sup>2</sup> dose  
9 achieved the 50 percent ACR response, while negligible  
10 numbers of placebo patients achieved a 50 percent ACR  
11 response.

12 Rapid decreases in the number of tender and  
13 swollen joints occurred with Enbrel treatment. A clear  
14 dose response was seen, with the most marked decline in  
15 joint counts seen with treatment with the 16 mg/m<sup>2</sup> dose.  
16 When the study was concluded at 3 months and Enbrel was  
17 discontinued, the joint counts returned toward baseline  
18 values within 2 to 6 weeks, consistent with the half-life  
19 of Enbrel of 3.5 days and reflects the reversal of Enbrel's  
20 effects once it is discontinued.

21 Consistent improvement was seen by all  
22 individual measures of disease activity. Patients in the  
23 placebo and the lowest-dose Enbrel groups showed minimal  
24 improvement, and patients who were in the highest dose, 16  
25 mg/m<sup>2</sup>, showed significant improvements which were quite

1 consistent in all of these variables.

2 Mean values for the various parameters used to  
3 assess disease activity are shown here for the placebo  
4 group and the 16 mg/m<sup>2</sup> group at baseline and at the end of  
5 the trial, at 3 months. The average patient had quite  
6 active disease at baseline. For example, they had  
7 approximately 30 tender and 24 swollen joints at baseline,  
8 their mean pain score was over 6 on a scale of 0 to 10,  
9 morning stiffness was approximately 5 hours, and the CRP  
10 was over 3 milligrams per deciliter. By the end of the  
11 study, the placebo group was relatively unchanged from  
12 baseline; however, the patients treated with Enbrel were  
13 significantly improved. The mean number of tender joints  
14 decreased to 13, the mean number of swollen joints  
15 decreased to 11, the mean pain score fell to 3.1, morning  
16 stiffness fell to just over an hour, and the CRP was near  
17 normal, at 1.1 milligrams per deciliter.

18 The next study I'll discuss is Protocol  
19 16.0009. The study design for this randomized, double-  
20 blind, placebo-controlled trial was very similar to that of  
21 16.0004, with some important differences. This was a 6-  
22 month trial, Enbrel was administered as a fixed dose, and  
23 independent blinded joint assessors performed all the joint  
24 counts. These blinded joint assessors were not involved  
25 with the other assessments of patients and, therefore, are

1 blinded to the adverse events and the clinical status of  
2 patients.

3           Enbrel was administered at a fixed dose of 10  
4 or 25 milligrams, given subcutaneously twice weekly. The  
5 25-milligram dose is approximately 16 mg/m<sup>2</sup>, the dose  
6 tested in Protocol 16.0004. The 10-milligram dose was  
7 chosen to be slightly higher than the intermediate dose  
8 tested in Protocol 16.0004. Two hundred and thirty-four  
9 patients at 13 sites were enrolled and received study drug.

10           The inclusion criteria for this trial were very  
11 similar to the inclusion criteria in Protocol 16.0004.  
12 Patients had to have failed from one to four DMARDs and  
13 have active rheumatoid arthritis at screening. They were  
14 allowed to be on stable doses of prednisone and NSAIDs. If  
15 patients were on a DMARD at study screening, the DMARDs  
16 were discontinued for at least a month prior to study drug  
17 administration.

18           The primary endpoint for Protocol 16.0009 was a  
19 20 percent ACR response at 3 months. Other endpoints  
20 included the 20 percent ACR response at 6 months, higher  
21 levels of response at 3 and 6 months, all of the components  
22 of the ACR response criteria, morning stiffness, the HAQ,  
23 and the SF-36. An intent-to-treat analysis was performed  
24 for the ACR endpoint. For the primary endpoint, the 20  
25 percent ACR response at 3 months, a patient was declared a

1 non-responder not only if they did not meet the ACR  
2 criteria at 3 months, but also if they withdrew for any  
3 reason prior to 3 months. For all other parameters, a  
4 last-observation-carried-forward analysis was performed.

5 The demographics and disease characteristics of  
6 the patients in this trial were very similar to the  
7 patients in 16.0004. The typical patient was, again, a  
8 woman in her 50s diagnosed with RA 11 to 13 years earlier,  
9 in her late 30s to early 40s. The average patient had  
10 already been treated with and failed over three DMARDs,  
11 including methotrexate. At the time of screening,  
12 approximately 45 percent of patients were on a DMARD, and  
13 55 percent of patients were not on a DMARD.

14 As in Protocol 16.0004, the majority of  
15 patients in the Enbrel group completed the full trial.  
16 More of the patients in the 25-milligram group completed  
17 the study than in the 10-milligram dose group. Far fewer  
18 patients in the placebo group completed the full 6-month  
19 study. In fact, the median time on the study in the  
20 placebo group was only 2.5 months. The primary reason for  
21 early discontinuation in the trial was lack of efficacy,  
22 with other reasons for discontinuation being similarly  
23 distributed among the groups.

24 The primary endpoint, the 20 percent ACR  
25 response at 3 months, was reached with statistical

1 significance. Onset of responses in the treatment group  
2 was rapid. As you can see, after 1 month on trial, 49  
3 percent of the patients in the 25-milligram group achieved  
4 the 20 percent ACR response. The 10-milligram group was  
5 also significantly improved compared to placebo; however,  
6 the responses at the 10-milligram dose were less rapid.

7 The difference between the 10- and the 25-  
8 milligram dose levels are most clearly seen at the higher  
9 levels of ACR response, as shown here. Forty percent of  
10 patients in the 25-milligram group achieved a 50 percent  
11 ACR response by 6 months compared to only 24 percent of the  
12 patients in the 10-milligram group. Both doses, though,  
13 were significantly better than placebo, with negligible 50  
14 percent ACR response rates.

15 The same pattern in joint count improvement was  
16 seen in this study as was seen in Protocol 16.0004, a rapid  
17 decline in the number of tender and swollen joints seen  
18 within the first month of treatment, with significant  
19 improvement in the Enbrel treatment group compared to the  
20 placebo group.

21 This slide shows the mean percent improvement  
22 in all the components of the ACR response rate. Both  
23 Enbrel groups were significantly improved compared to the  
24 placebo group. The magnitude of the response is greatest  
25 with the 25-milligram dose.

1           Mean values of these parameters reflect the  
2 marked improvement seen with Enbrel treatment. In  
3 contrast, the placebo group remained unchanged or became  
4 worse during the trial. At 6 months, in the group treated  
5 with the 25-milligram dose of Enbrel, the mean number of  
6 tender joints improved from 33 to 15, the mean number of  
7 swollen joints improved from 25 to 12, and also at 6 months  
8 the average patient treated with 25 milligrams had a  
9 significant decrease in pain, from 6.7 to 3.1, had a  
10 significant improvement in physical function, with the  
11 disability index dropping from 1.6 to 1. These subjective  
12 clinical improvements were paralleled by the substantial  
13 improvement in the laboratory markers of inflammation, with  
14 the ESR normalizing, the CRP nearing normal, going from 4.7  
15 to 2.2 milligrams per deciliter.

16           Now I'd like to move on to the last of the  
17 placebo-controlled trials, Study 16.0014. This was a 6-  
18 month double-blind, randomized, placebo-controlled trial in  
19 which patients were randomized to receive placebo plus  
20 methotrexate or Enbrel plus methotrexate. The methotrexate  
21 doses these patients were receiving were not trivial and  
22 ranged from 12.5 to 25 milligrams per week. Patients  
23 received 25 milligrams of Enbrel subcutaneously twice  
24 weekly for 6 months, and 89 patients were enrolled at seven  
25 sites. Unlike the other trials, where a 1:1 randomization

1 ratio was used, in this trial, for every one placebo  
2 patient that was treated, two Enbrel-treated patients were  
3 treated. Therefore, 30 patients received placebo plus  
4 methotrexate, and 59 patients received Enbrel plus  
5 methotrexate.

6 To be eligible, patients had to have at least  
7 six swollen and six tender joints. They were on  
8 methotrexate for at least 6 months, with stable doses for  
9 the last 4 weeks. Patients were allowed to be on stable  
10 prednisone and NSAIDs during the trial.

11 The primary endpoint was the 20 percent ACR  
12 response rate at 6 months. The other endpoints are shown.  
13 An intent-to-treat analysis was performed for the ACR  
14 responses. A last-observation-carried-forward analysis was  
15 performed for the other endpoints.

16 The average patient was in their late 40s or  
17 early 50s, female, and had been diagnosed with rheumatoid  
18 arthritis 13 years earlier. She had been treated with over  
19 two prior DMARDs and was receiving methotrexate,  
20 corticosteroids, and NSAIDs.

21 The majority of patients completed the full 6-  
22 month trial, 97 percent of the patients on Enbrel and 80  
23 percent of the patients in the placebo group. For the  
24 Enbrel treatment group, the 97 percent completion rate  
25 translates into 57 of the 59 patients completing the full 6

1 months of therapy. The primary reason for discontinuation  
2 in the placebo-plus-methotrexate group was lack of  
3 efficacy.

4 The two groups were comparable in distribution  
5 of methotrexate doses. The majority of patients in either  
6 group were treated with from 15 to 25 milligrams of  
7 methotrexate per week.

8 Shown on the next few slides are the ACR  
9 responses. Significantly higher response rates were seen  
10 in the group receiving Enbrel plus methotrexate compared to  
11 the group receiving placebo plus methotrexate. The  
12 responses were rapid, with 56 percent of patients in the  
13 Enbrel-plus-methotrexate group achieving a 20 percent ACR  
14 response by 1 month. By 6 months, 71 percent of the  
15 patients in the Enbrel-plus-methotrexate group achieved a  
16 20 percent ACR response. The primary endpoint, the 20  
17 percent ACR response rate at 6 months, was reached.

18 As for higher levels of response, by 6 months,  
19 approximately 40 percent of patients treated with the  
20 combination of Enbrel plus methotrexate achieved a 50  
21 percent ACR response compared to only 3 percent of  
22 patients, or 1 patient, on placebo plus methotrexate.

23 Early, rapid improvements in joint count were  
24 again observed with Enbrel treatment.

25 Consistent significant improvement of disease

1 by all measures of disease activity was seen, as assessed  
2 by the mean percent change from baseline to 6 months.  
3 Enbrel-treated patients -- and these were patients on  
4 methotrexate for at least 6 months prior to baseline  
5 assessment -- had substantial improvement in their RA  
6 compared to baseline.

7           The mean values of these parameters reflect  
8 these significant improvements. In the Enbrel-plus-  
9 methotrexate group, the mean number of tender joints  
10 improved from 28 to 11, the mean number of swollen joints  
11 improved from 21 to 7. At 6 months, the average patient's  
12 pain score fell from 5.1 to 2.3. Physical function  
13 improved, with the disability index falling from 1.5 to 0.9  
14 and the CRP dropping from 2.9 to 1.2 milligrams per  
15 deciliter.

16           One quite remarkable aspect of Enbrel therapy  
17 is how predictable and consistent the responses have been.  
18 The consistency of response is demonstrated not only in the  
19 randomized, placebo-controlled trials, 16.0004, 16.0009,  
20 and 16.0014, but also in open-label studies. Study 16.0019  
21 was an open-label trial in 239 adult patients with active  
22 RA, all of whom received 25 milligrams of Enbrel  
23 subcutaneously twice weekly for 6 months. The entry  
24 criteria for this study were the same as for Protocol  
25 16.0009. Study 16.0016 was a study in 69 pediatric

1 patients with active JRA, all of whom had an inadequate  
2 response to methotrexate. The first 3 months of this study  
3 evaluated open-label Enbrel. These children received  
4 Enbrel at a dose of 0.4 milligrams per kilo, equivalent to  
5 the 25-milligram dose in adults.

6 In the open-label studies, as well as the  
7 placebo-controlled trials, the 20 percent ACR response  
8 ranged from 62 to 75 percent. As a point of clarification,  
9 what's shown on this slide for the JRA study is actually  
10 the 30 percent JRA definition of improvement score in place  
11 of the 20 percent response rate. As you can see, 74  
12 percent of these children reached the 30 percent JRA  
13 response.

14 To evaluate sustained response, we assessed the  
15 responses of patients treated in Protocol 16.0009. These  
16 patients moved directly into an open-label, long-term  
17 treatment trial once 16.0009 was complete. Displayed will  
18 be the responses of patients observed at each time point.  
19 The last-observation-carried-forward analysis was not used  
20 here; however, very few patients have withdrawn from 6  
21 months onward. Actually, only 10 patients.

22 The 20 percent ACR response is sustained  
23 through 18 months of treatment. The 50 percent ACR  
24 response is sustained through 18 months of treatment as  
25 well.

1                   Consistent efficacy is seen with Enbrel  
2 treatment in all subgroups analyzed and in objective  
3 laboratory tests. There was consistent benefit in all the  
4 patient subgroups. Males and females, Caucasians and non-  
5 Caucasians, patients of various ages, of various body size,  
6 with either elevated or normal baseline levels of CRP, ESR,  
7 or rheumatoid factor, who had rheumatoid arthritis for  
8 various lengths of time from under 5 years to over 10  
9 years, from study sites with low or high enrollment, who  
10 were or were not receiving steroids or NSAIDs, who were or  
11 were not withdrawn from DMARDs, and who had various numbers  
12 of active joints at baseline all responded to Enbrel  
13 treatment.

14                   The objective laboratory measurements also  
15 support the benefits seen with Enbrel. Consistent  
16 improvement in the ESR was seen. The mean levels of ESR  
17 decreased in a dose-dependent fashion, mirroring the  
18 clinical improvements. The lowest ESRs were seen with the  
19 25-milligram dose of Enbrel. The mean levels of CRP also  
20 decreased in a dose-dependent fashion with Enbrel  
21 treatment.

22                   We also looked at how the patients felt.  
23 Improvement in physical function and health-related quality  
24 of life was assessed in the controlled trials by the HAQ  
25 and the SF-36 questionnaires. The HAQ was assessed in all

1 three controlled trials, and the disability index of the  
2 HAQ was used to assess physical function. Health-related  
3 quality of life was assessed by the two validated questions  
4 in the full HAQ, one of which assesses arthritis-specific  
5 health status, and the other assesses the general health  
6 status. In addition, this version of the HAQ also included  
7 all questions from the vitality and the mental health  
8 domains of the SF-36.

9 The HAQ questionnaire was administered serially  
10 in these studies. Due to changing guidelines, the SF-36  
11 was included in Protocol 16.0009, but was introduced after  
12 the study was already open for enrollment. Due to a very  
13 rapid enrollment in this study, it was administered at  
14 baseline in 48 of the 234 patients.

15 I'd like to take a moment to review the format  
16 of this slide, as this format will be shown multiple times  
17 to display the HAQ data. On the left panel, the mean  
18 values for the various indices will be shown at baseline  
19 and at the end of the study for each of the trials. On the  
20 right panel, the mean percent improvement from baseline to  
21 the end of the trial is graphically displayed.

22 As you can see, Enbrel treatment significantly  
23 improved the physical function of these patients. The  
24 patients were comparable at baseline. The average Enbrel-  
25 treated patient reported anywhere from a 27 percent

1 improvement in physical function at 3 months in Protocol  
2 16.0004 to a 39 to 44 percent improvement at 6 months in  
3 Protocol 16.0009 and 16.0014, markedly superior to the  
4 responses seen in the placebo groups.

5 Another way of quantifying the improvement in  
6 physical function is by analyzing the percent of patients  
7 with an improvement in the disability index of 0.5 units or  
8 greater. As you know, the disability index ranges from 0,  
9 being the best, to the 3, being the worst. The analysis  
10 shown here could be performed for two of the controlled  
11 trials, Protocol 16.0009 and Protocol 16.0014. At 6  
12 months, more than 50 percent of patients had an improvement  
13 in the disability index of 0.5 units or greater.

14 Now I'll speak about health-related quality of  
15 life. Significant improvements in arthritis-specific  
16 health status were seen with Enbrel treatment. The mean  
17 values for placebo and 25-milligram patients, shown on the  
18 left panel, were very similar at baseline, ranging from 60  
19 to 62 in Protocol 16.0009 to 51 to 54 in Protocol 16.0014,  
20 with 1 being the best score and 100 being the worst score.  
21 The typical Enbrel patient had a significant improvement  
22 from baseline, approximately 45 percent. The placebo-  
23 treated group was unchanged or actually worsened from  
24 baseline.

25 Significant improvements in general health

1 status were also seen. Of all the health-related quality  
2 of life assessments that I'll discuss, this is the only one  
3 where the scale is reversed. One hundred is best and 1 is  
4 worst. Again, the groups were very similar at baseline.  
5 With Enbrel treatment, there was a 33 to 51 percent  
6 improvement in general health status. The placebo-treated  
7 patients were unchanged or worse than from baseline.

8 Significant improvements in vitality were also  
9 seen. The placebo and Enbrel groups were well balanced at  
10 baseline, with mean baseline scores ranging from 60 to 69  
11 in the two protocols. Enbrel-treated patients had  
12 improvements in vitality of approximately 25 to 30 percent,  
13 while the placebo group was relatively unchanged.

14 Approximately 35 percent improvement in mental  
15 health was seen with Enbrel treatment. Typical questions  
16 asked of patients to assess mental health include judgments  
17 of happiness and well-being. The placebo groups were  
18 relatively unchanged from baseline.

19 As for the SF-36 questionnaire, as stated  
20 earlier, it was added to Protocol 16.0009 after study  
21 initiation, and 48 of the 234 patients in the trial had the  
22 questionnaire administered from baseline and throughout the  
23 study, approximately equal numbers in each of the three  
24 treatment groups. However, and importantly, the results of  
25 the SF-36 and the HAQ correlated well.

1           Improvement in physical function was sustained  
2 over long-term treatment. This can again be assessed by  
3 observing the continued responses of patients from Protocol  
4 16.0009 who moved directly into a long-term treatment trial  
5 once Protocol 16.0009 was completed. Improvement in  
6 physical function was sustained for up to 18 months.  
7 Improvement in health-related quality of life was also  
8 sustained for up to 18 months.

9           Shown here is the sustained benefit in general  
10 health. Similar sustained benefit is seen for all other  
11 assessments of health-related quality of life.

12           The 70 percent ACR responses were also analyzed  
13 in the controlled trial. Significantly more patients  
14 treated with Enbrel achieved a 70 percent ACR response than  
15 patients treated with placebo. From 15 to 20 percent of  
16 Enbrel-treated patients in the controlled trial achieved a  
17 70 percent ACR response compared to 0 to 2 percent of  
18 patients in the placebo groups. The average patient with a  
19 70 percent ACR response had a tender joint count of 28 and  
20 a swollen joint count of 20 at baseline. These dropped to  
21 two and three by the end of the study. Improvement in the  
22 70 percent ACR response was sustained for 18 months.

23           To summarize efficacy, Enbrel treatment  
24 significantly reduces the signs and symptoms of active  
25 rheumatoid arthritis. It decreases disease activity and

1 consistently benefits all patient subgroups. The  
2 improvement is rapid and is sustained with continued Enbrel  
3 treatment. Enbrel therapy significantly improves physical  
4 function and health-related quality of life. There was  
5 consistent improvement seen in all questionnaires  
6 administered, both the HAQ and the SF-36. Improvements  
7 were rapid and were sustained with continued Enbrel  
8 treatment. Patients treated with Enbrel achieved high  
9 levels of response. Seventy percent ACR responses were  
10 achieved in 15 to 20 percent of patients and were sustained  
11 with continued treatment, and for all of the above, Enbrel  
12 alone was effective, as well as Enbrel in combination with  
13 methotrexate.

14 I'd like now to turn from the efficacy of  
15 Enbrel to its safety. The total number of patients treated  
16 with Enbrel for all indications is shown here. Thirteen  
17 hundred and eighty-one patients have received Enbrel in all  
18 clinical trials, and the majority of them, 1,039, have been  
19 patients with rheumatoid arthritis. Seven hundred and  
20 thirty-three patients with rheumatoid arthritis have  
21 received Enbrel for at least 6 months, 194 have received  
22 Enbrel for at least 12 months or more, 87 patients at this  
23 point have been treated for at least 18 months, and 22  
24 patients have received Enbrel therapy for 24 months. The  
25 size of this safety database meets the ICH guidelines.

1 All of my comments today on safety will be  
2 focused on data in 745 RA patients, excluding data from an  
3 ongoing blinded Phase III trial of Enbrel versus  
4 methotrexate in patients with early rheumatoid arthritis.  
5 However, although the study is still blinded, a blinded  
6 analysis for safety has shown a safety profile in that  
7 study that is similar to the profile you'll see in today's  
8 presentations.

9 One of the considerations in assessing the  
10 safety data was how to account for the much longer  
11 observation period in the Enbrel treatment group compared  
12 to the placebo group. As shown on this slide, fewer  
13 placebo patients remained on the controlled trial for the  
14 entire duration of the study. The disparity in time on  
15 trial is shown. The placebo group was on study for a far  
16 shorter period of time in both Protocol 16.0004 and 16.0009  
17 compared to Enbrel-treated patients. In Protocol 16.0014,  
18 Enbrel and placebo patients were on the study for an  
19 equivalent period of time. This is the study with  
20 background methotrexate.

21 In order to account for this, the safety  
22 analyses are presented both in crude rates, the percent of  
23 patients experiencing an event, as well as the number of  
24 events per patient-year of exposure, which takes into  
25 account the longer observation period seen in the Enbrel

1 treatment group. The patient-years in each group were  
2 calculated by summing the days from the first to the last  
3 dose within a study, summed over all studies for which  
4 patients participated, and then dividing that number by  
5 365. In most of the following slides, both the crude rate  
6 and the events per patient-year will be displayed.

7 Safety in the controlled trials will be  
8 discussed first, reviewing these topics. The adverse  
9 events in controlled trials are shown here. Injection site  
10 reactions occurred more frequently with Enbrel treatment.  
11 All other adverse events, including infections, headaches,  
12 and gastrointestinal symptoms, occurred with a similar  
13 frequency in the two groups when the events-per-person-year  
14 analysis was utilized. As physicians may be particularly  
15 interested in the safety profile of Enbrel in combination  
16 with methotrexate, the adverse events from this trial have  
17 been separated out.

18 Aside from a higher frequency of injection site  
19 reactions in the Enbrel group, the adverse events in the  
20 two groups were similar. Specifically, there was no  
21 increase in liver toxicity, in GI symptoms, or infections  
22 in the treatment group with Enbrel plus methotrexate.

23 The injection site reactions were graded  
24 according to the NCI common toxicity scale. Grade 1 was  
25 defined as redness alone; Grade 2 was an injection site

1 reaction associated with pain, swelling or itching, with or  
2 without redness; Grade 3 was defined as ulceration; and  
3 Grade 4 was defined as requiring plastic surgery. All of  
4 the patients who had injection site reactions had either  
5 Grade 1 or Grade 2 injection site reactions.

6 It should be noted that over half the patients  
7 on Enbrel did not have a single injection site reaction.  
8 Of the other patients who had an injection site reaction,  
9 most had five or fewer during their entire treatment  
10 course, five injection site reactions or fewer out of an  
11 average of 40 injections.

12 When looking over all injections given,  
13 injection site reactions were associated with only 5  
14 percent of injections. Injection site reactions were mild,  
15 either Grade 1 or Grade 2. Most patients had injection  
16 site reactions within the first 4 weeks of treatment. In  
17 the remaining months, approximately 5 percent or fewer  
18 patients had an injection site reaction.

19 Infections. We carefully collected all  
20 infection data and in Protocol 16.0009 and 16.0014 used a  
21 separate form to capture detailed information on every  
22 infection. Infections reported using the detailed  
23 infection form from these two controlled trials are shown  
24 here. The majority of infections seen were common  
25 outpatient infections, such as upper respiratory tract

1 infections or sinusitis. No Enbrel-treated patients  
2 discontinued from the controlled trials because of an  
3 infection. Of note, there was no increase in the rate of  
4 URIs when the different observation times in the placebo  
5 and Enbrel groups were accounted for.

6 Moving from the most frequent infections to  
7 medically important infections, no increase in medically  
8 important infections was seen with Enbrel treatment. Shown  
9 here are the medically important infections in the  
10 controlled trials, and the definition of a medically  
11 important infection was an infection treated with IV  
12 antibiotics or treated in the hospital. Two placebo  
13 patients, one patient in the lowest Enbrel group, and two  
14 in the 25-milligram dose group had medically important  
15 infections.

16 Displayed here are the other events which could  
17 be considered medically important. The categories are  
18 shown on the left-hand side, and shown horizontally across  
19 the table, the column headings are divided to show the  
20 placebo group and the various dose groups of Enbrel, moving  
21 from the lowest-dose group to the highest. The numbers in  
22 the table represent the percent of patients experiencing a  
23 specific event during the controlled trials. As you can  
24 see, very few medically important events occurred, and no  
25 dose response was evident.

1                   Routine laboratory testing for liver function  
2 tests, hematology, creatinine, BUN, and urinalysis were  
3 performed. No laboratory abnormalities were associated  
4 with Enbrel therapy. Specifically, no pattern of liver  
5 function test elevations, anemia, or renal function  
6 abnormalities were seen.

7                   Moving to the safety analysis of all studies,  
8 placebo-controlled and open-label trials, I'll first review  
9 the analysis of adverse events in patient subgroups, and  
10 then discuss categories of medically important adverse  
11 events.

12                   The safety profile of Enbrel in older and  
13 younger patients was similar to that seen for all Enbrel-  
14 treated patients. As one would expect, children had more  
15 GI complaints and infections such as otitis media than  
16 adults, but these were not greater than one would expect  
17 for this age group.

18                   No increase in mortality was seen with Enbrel  
19 treatment. Out of 745 patients, three Enbrel-treated  
20 patients died, the same percentage in the placebo and the  
21 Enbrel-treated groups.

22                   When the safety experience in all RA patients  
23 was analyzed, no increase in medically important infections  
24 was seen with Enbrel. These infections are fully outlined  
25 in your briefing document. Twenty-two medically important

1 infections occurred in 20 patients out of 745 Enbrel-  
2 treated patients. As you recall, no placebo group was  
3 available for comparison after 6 months. The infections  
4 reported were those commonly seen in RA patients. The  
5 clinical course of these infections was not unusual, and  
6 Enbrel was continued through 15 of these infections. All  
7 infections resolved but one. This patient had  
8 polyarticular septic arthritis and died of complications of  
9 staph aureus sepsis. Mortality in RA patients with  
10 polyarticular septic arthritis is approximately 50 percent.  
11 This patient had all the risk factors for a poor prognosis.

12 There was no evidence that medically important  
13 infections increased with increasing exposure to Enbrel.  
14 The frequency of infections occurred consistently in 1 to 2  
15 percent of patients in each 6-month interval of exposure to  
16 Enbrel.

17 To summarize infections, there was no evidence  
18 of an increased frequency or severity of infections, nor  
19 increased mortality from infections occurring with Enbrel  
20 treatment. There was no evidence of an increased number of  
21 infections with increased Enbrel exposure.

22 Cancer. No increase in cancer rate was seen  
23 with Enbrel treatment. Seven patients treated with Enbrel  
24 and one patient on placebo had cancer diagnosed while on  
25 study. We calculated the expected number of cancers in the

1 patients in our database using the rates from the NIH SEER  
2 national database. The NIH SEER database provides cancer  
3 rates for the general population. We found that we would  
4 have expected to have seen 6.4 patients with cancer in the  
5 Enbrel treatment group and approximately one placebo  
6 patient with cancer, just what was observed. A variety of  
7 different solid tumors was seen in line with the most  
8 common cancers in the general population, including breast,  
9 lung, ovarian, prostate, and Hodgkin's disease. One case  
10 of bile duct carcinoma was also seen.

11 Antibody to Enbrel. In RA studies, patients  
12 were screened with an ELISA. None of the placebo patients  
13 were positive by this assay, and 1 percent, or six, of the  
14 Enbrel patients were positive. These samples were then  
15 tested for neutralizing antibody. As you would expect from  
16 the clinical results, no neutralizing antibody was  
17 detected. Four of the six ELISA-positive patients continue  
18 presently on Enbrel therapy, with continued disease  
19 response and no unexpected adverse events.

20 Autoantibodies. Double-stranded DNA, ANA, and  
21 anticardiolipin IgG and IgM assays were performed at  
22 baseline and every 3 to 6 months in Protocol 16.0009 and  
23 16.0014. Most patients were negative for autoantibodies at  
24 baseline and remained negative. Variable low-level  
25 fluctuations were seen with all assays in both placebo and

1 Enbrel groups. By the most specific assay for double-  
2 stranded DNA, the crithidia assay, the only patient  
3 consistently positive was the patient with lupus prior to  
4 study start. What may be most important, however, is that  
5 no patients developed lupus or any other new rheumatic  
6 autoimmune disease, and none of the patients positive for  
7 ACLA had a thrombotic event or thrombocytopenia.

8 Testing for immune function was performed in 49  
9 patients in Protocol 16.0009. There was no evidence that  
10 Enbrel therapy suppressed immunity compared to placebo.  
11 Delayed-type hypersensitivity was evaluated, as well as a  
12 number of various white blood cell subtypes,  
13 lymphoproliferation, neutrophil function, and quantitative  
14 immunoglobulin. No suppression of immune function was seen  
15 with Enbrel.

16 As it is important to continue to assess the  
17 safety of any new therapeutic, in addition to the routine  
18 spontaneous adverse event reporting system, we also have in  
19 place a plan for long-term safety monitoring. All patients  
20 who have been treated in previous RA clinical trials, those  
21 who received Enbrel as well as those who received placebo,  
22 have been offered a chance to participate in a long-term  
23 treatment trial, Protocol 16.0018. Six hundred and thirty-  
24 six of approximately 1,200 patients who will be eligible  
25 are currently enrolled in this study. The remainder are

1 expected to join once the studies they are currently  
2 participating in are completed. Safety data will be  
3 actively collected on patients who continue Enbrel, as well  
4 as patients who, for whatever reason, stop taking Enbrel  
5 after any amount of time on this trial.

6 Our long-term safety data will be compared with  
7 three different databases: a newly formed disease- and  
8 age-matched RA cohort of 400 patients, an already  
9 established RA cohort from Olmsted County of 425 patients,  
10 and the NIH SEER database, which will be utilized to assess  
11 cancer rates. Using this approach, we will have the  
12 ability to detect small increases in serious rare events.  
13 Using the database most comparable to the Enbrel database,  
14 the Olmsted County database, with 1 and a half additional  
15 years in a long-term trial, we will have good power to  
16 detect even small increases in the incidence of serious  
17 rare events -- cancer, deaths, and hospitalizations. We  
18 are in the process of determining the power to detect  
19 medically important infections in the Olmsted County  
20 database, but we expect we will have good power to detect  
21 small increases in this event also.

22 To summarize safety, in 1,039 patients with RA,  
23 the 745 patients discussed in detail and the others in an  
24 ongoing blinded trial, Enbrel was very well tolerated. No  
25 major safety events were associated with Enbrel treatment.

1 We are committed to long-term safety monitoring and are  
2 actively collecting and analyzing additional long-term  
3 safety data.

4 I'd like now to turn the platform over to Dr.  
5 Ann Hayes, who will give some concluding remarks and  
6 moderate questions.

7 DR. HAYES: Thank you, Leslie.

8 Rheumatoid arthritis is a chronic disease which  
9 is associated with significant long-term morbidity.  
10 However, for the patient with active rheumatoid arthritis,  
11 this is an active and painful disease that affects everyday  
12 life. Although there are various therapies available for  
13 active rheumatoid arthritis, the need for new therapy is  
14 ever present. Based on the data presented today and  
15 expanded upon in your briefing document, Enbrel offers a  
16 new class of agents in the armamentarium of anti-rheumatic  
17 therapy.

18 The risk/benefit for Enbrel compares very  
19 favorably to other agents which are currently approved for  
20 this disease. Enbrel provides a targeted anticytokine  
21 therapy which enhances the body's normal mechanism for  
22 blocking the activity of TNF. Like the normal soluble  
23 receptor, Enbrel does not interfere with the body's normal  
24 production of TNF. Unlike some other therapeutic agents  
25 used in rheumatoid arthritis, Enbrel is not a non-specific

1 suppressor of immune function.

2           Because of the theoretical concerns that  
3 blocking TNF would cause general immunosuppression or non-  
4 reversible suppression of body defenses, we have carefully  
5 and specifically monitored our patients. We know from  
6 Study 16.0004 that discontinuation of Enbrel results in  
7 return of the signs and symptoms of rheumatoid arthritis  
8 within a relatively rapid period of time, indicating that  
9 the effect of Enbrel on TNF is reversible. We have also  
10 evaluated lymphocyte function and neutrophil function in a  
11 subset of our patients on 16.0009 and have been unable to  
12 show any abnormalities compared to the placebo groups, with  
13 more than 6 months of uninterrupted twice weekly therapy.

14           The only adverse event that without question is  
15 associated with Enbrel therapy is injection site reactions.  
16 These occur in fewer than half of the patients, they occur  
17 with less than 5 percent of the injections, and they have  
18 all been mild. Most importantly, they have not resulted in  
19 patients discontinuing from therapy. No other adverse  
20 event has occurred with either increased frequency over  
21 that seen in placebo groups or over that expected in the  
22 general RA population.

23           Specifically, as Dr. Garrison has indicated,  
24 infections have not occurred at an increased rate, nor have  
25 they become more frequent with prolonged exposure to

1 Enbrel. The rate of upper respiratory infections, the most  
2 common infection that was seen, is not greater than that  
3 expected in the normal adult population, where one expects  
4 an adult to have between two and four colds per year. Only  
5 22 infections which required either hospitalization or  
6 intravenous antibiotics were seen in 745 patients followed  
7 for 491 patient-years. Twenty-one of these 22 infections  
8 resolved without long-term sequelae, and 15 of these  
9 patients did continue Enbrel throughout their entire course  
10 of infection.

11 One patient did, however, die of sepsis as a  
12 complication of septic arthritis. Although our data does  
13 not indicate an increased rate of severity or infection, we  
14 do feel it would be prudent to label Enbrel indicating that  
15 in the face of a serious infection or impending sepsis  
16 syndrome, the drug should be interrupted until the  
17 infection resolves.

18 Another area of theoretical concern about the  
19 inhibition of TNF is the area of cancer. Malignancies are  
20 known to occur with an increased frequency in patients with  
21 rheumatoid arthritis. The types of cancer and the  
22 incidence of cancer that we have observed are comparable to  
23 that of the SEER database for the normal national  
24 population. The time to diagnosis of these malignancies  
25 has not been clustered late in the treatment with Enbrel,

1 but has been seen throughout all points of time on study.

2 Another concern 2 or 3 years ago, when we were  
3 designing these trials, was whether or not blocking TNF  
4 would result in the production of autoantibodies and other  
5 autoimmune disease. This was based on suggestions from  
6 preclinical data and on a couple of patients who had been  
7 treated with other anti-TNF therapies who developed lupus-  
8 like syndromes. Part of the problem with these studies is  
9 that, for the first time, patients with rheumatoid  
10 arthritis are being serially and frequently assessed with  
11 lab markers which, under normal circumstances, are done in  
12 the face of a clinical indication. However, because of the  
13 concern of this, we did serially evaluate our patients for  
14 double-stranded DNA, ANA, and ACLA. The patients with  
15 Enbrel and over 100 patients on placebo have been tested.  
16 The results have revealed no pattern of consistent  
17 positivity associated with Enbrel, and as Dr. Garrison has  
18 said, more importantly, we have not observed any clinical  
19 evidence in any patient of systemic lupus or any other  
20 autoimmune disease.

21 Dr. Garrison has indicated that Immunex is  
22 committed to a long-term study to monitor our patient  
23 population for these potential long-term effects and other  
24 events that might occur. We recognize that as with any new  
25 therapy for a chronic disease, continued monitoring is

1 essential. Our study is already in place, with more than  
2 600 patients already entered into the long-term follow-up,  
3 with a projected total population of 1,200. The  
4 tolerability of this therapy and its acceptance by patients  
5 is reflected by the fact that up to 90 percent of patients  
6 who have been eligible to enter our long-term trial have  
7 chosen to do so. This is not a requirement. Patients are  
8 offered this opportunity, and as I say, up to 90 percent of  
9 patients have chosen to do so.

10 We now have nearly 200 patients who have been  
11 dosing in an uninterrupted twice weekly fashion with this  
12 product for over 1 year, with many patients who have  
13 received uninterrupted twice weekly dosing of Enbrel for up  
14 to 2 years. The treatment benefit for patients has shown  
15 remarkable consistency across all trials, whether they be  
16 open-label or controlled. Responses have occurred in all  
17 measures of disease activity that comprise the ACR  
18 responses, as well as quality of life issues which reflect  
19 the patient's own sense of well-being. All subgroups of  
20 patients tested have responded equally to this therapy.  
21 Patients have responded rapidly, often within two to four  
22 doses of receiving Enbrel. A significant proportion of  
23 patients, 15 to 20 percent, have achieved an ACR 70 percent  
24 response rate, and all subgroups of patients studied have  
25 continued to sustain these responses as long as they have

1 remained on Enbrel therapy.

2           Enbrel offers to patients with active, poorly  
3 controlled rheumatoid arthritis a new therapy option that  
4 has a high potential for producing rapid and significant  
5 disease benefit with a very acceptable and manageable  
6 adverse event profile. Based on this data, we propose that  
7 Enbrel be approved for the treatment of active rheumatoid  
8 arthritis. Enbrel decreases disease activity, it increases  
9 functional ability, and it improves quality of life.  
10 Enbrel is effective both alone and in combination with  
11 methotrexate. We would recommend that Enbrel be delivered  
12 subcutaneously twice a week at a flat dose of 25 milligrams  
13 per dose in the adult population.

14           This concludes Immunex' presentation of the  
15 data, and we would be happy to entertain questions.

16           DR. PETRI: Thank you.

17           I'm going to ask the panel to try to limit  
18 their questions to ones of clarification or to ask to see  
19 additional data, and not to try to anticipate this morning  
20 a discussion of questions that will occur this afternoon.

21           I'd like to start with several questions that I  
22 think may be best addressed to Dr. Garrison. The first is  
23 a question about her slide on consistent efficacy,  
24 specifically the subgroup that are rheumatoid factor-  
25 negative. I'd like to ask Dr. Garrison, is there in fact a

1 positive effect on the ACR response rate in that subgroup?

2 DR. GARRISON: As you can see here, we did an  
3 odds ratio analysis looking at baseline rheumatoid factor  
4 in all of the controlled trials, and there is a significant  
5 benefit for patients who have at baseline normal levels of  
6 rheumatoid factor, as well as patients who have elevated  
7 levels of rheumatoid factor.

8 I'd like to break that down study by study.  
9 This is the rheumatoid factor population and the 20 percent  
10 ACR response rate in each of the controlled trials,  
11 16.0004, 16.0009, and 16.0014. There were very few  
12 patients who were rheumatoid factor-negative in these  
13 studies. In this small subgroup of patients, as you can  
14 see, there appear to be higher responses with Enbrel  
15 treatment, aside from the 16.0009 trial, and in that trial,  
16 the placebo group had a 38 percent 20 percent ACR response.

17 I'd like to go to a higher level of response,  
18 and you can see the results there. With a 50 percent ACR  
19 response, the rheumatoid factor-negative population does  
20 still appear to respond to Enbrel treatment. However,  
21 again, this is a small subgroup that we studied.

22 DR. PETRI: Dr. Garrison, you may want to stay  
23 at the microphone, because my second question is about your  
24 slides on the autoantibodies. Specifically for  
25 anticardiolipin, can you show us the percent of patients

1 who were in the medium or high positive range using the  
2 international standards?

3 DR. GARRISON: Well, I'd like to show Slide J-  
4 6. This is in your briefing document also, and what was  
5 done here is, we've shown you some shift tables. You can  
6 see that baseline positive for anticardiolipin IgM ranges  
7 anywhere from 3 percent to 18 percent baseline for the two  
8 protocols, and there were patients shifting from negative  
9 to positive as well as positive to negative. Most of the  
10 positives that were seen were not high positives. They  
11 were close to the upper limit of normal.

12 DR. PETRI: Are you going to show us IgG as  
13 well?

14 DR. GARRISON: Sure, and IgG is J-5. Again,  
15 there was a very high baseline positive rate in the two  
16 studies, ranging from 7 percent to 23 percent. There were  
17 patients who became positive and became negative in all of  
18 the groups.

19 I'd like to show one other slide, and that's J-  
20 18. I didn't talk about the pediatric study in detail  
21 today. That will be the topic of a supplemental BLA.  
22 However, we found that it was very important, as others  
23 have found, to test these samples at the same time using  
24 exactly the same kit lots. You can see on the left-side  
25 panel, when we used different lots, we had much more

1 variability. When we used the same lots, there was much  
2 less variability. This was done consistently in the  
3 pediatric trial, but was not done in the adult trials and  
4 may have some effect on the variability of results that  
5 we've seen.

6 DR. PETRI: Dr. Garrison, I have one last  
7 question for clarification. Can you please show us the SF-  
8 36 results by subscales?

9 DR. GARRISON: I'm not prepared to do that  
10 today. Again, it was a small subset in each of the groups.  
11 However, I can show you one slide that outlines how  
12 consistent the results were and well correlated with the  
13 same subscales in HAQ as far as the mental health and  
14 vitality, if that will be helpful.

15 DR. PETRI: Why don't you go ahead and show  
16 that.

17 DR. GARRISON: Okay. That's Q-7. As I said  
18 before, all 234 patients completed the HAQ, and 48 patients  
19 completed the SF-36 from baseline, approximately 15  
20 patients in each of the three treatment groups. We were  
21 particularly interested in the mental health and vitality  
22 scales and how they correlated between the HAQ, which  
23 included all of those questions -- this particular full HAQ  
24 did include all these questions -- and how that correlated  
25 with those particular domains in the SF-36. So what we did

1 was, we looked at 984 SF-36 questionnaires from the 48  
2 patients who completed these questionnaires from baseline,  
3 and we compared those questionnaires to the HAQ  
4 questionnaires which were obtained at exactly the same time  
5 period, and the mental health and the vitality were very  
6 well correlated between SF-36 and the HAQ, with a Spearman  
7 correlation coefficient of 0.86.

8 DR. PETRI: Thank you.

9 Let me now ask for additional questions. Dr.  
10 Felson first.

11 DR. FELSON: Michelle took one of my  
12 clarification questions, but let me ask the other. The  
13 infection data that you presented here seems, at least on  
14 the face of it, to be at odds with data that's in the FDA's  
15 packet on the rates of infection in the trial. They show  
16 higher rates of upper respiratory and total infections.  
17 I'm wondering if you'd comment on that.

18 DR. HAYES: The data presented in the FDA  
19 briefing package that will be presented today does not take  
20 into account the duration of time on study. It's a direct  
21 incidence, and we have shown you both direct incidence and  
22 the rate per patient-year. As Dr. Garrison stated, the  
23 median time on study for our placebo patients was only 2.5  
24 months compared to a median of 6 months for the patients  
25 who were on Enbrel, which, if you're talking about having a

1       URI, gives you a tremendously increased probability of  
2       having one. So the data presented in the FDA briefing  
3       package does not take into account time on study.

4                You will also notice some number differences  
5       between the numbers in the FDA briefing package and ours.  
6       We had filed data with the FDA initially, and then we did a  
7       4-month safety update. Our numbers, for instance, of 22  
8       medically important infections versus 19 is because of  
9       three more infections in that safety data update. So we're  
10      really not at odds, it's just we included more data from  
11      our safety update than is included -- the patients are  
12      exactly the same patients, as Dr. Siegel will discuss.

13               I believe that's correct, Dr. Siegel. I hope  
14      I'm not speaking out of turn.

15               DR. JEFF SIEGEL: Yes.

16               DR. PETRI: Thank you.

17               Dr. Abramson?

18               DR. ABRAMSON: I had two clarification  
19      questions. One was a technical one. You said that there  
20      was no effect on leukocyte functions, I guess, Dr.  
21      Garrison. That's very difficult to tell ex vivo.  
22      Particularly tumor necrosis factor has very little effect  
23      on white cells, except that it primes neutrophils for  
24      oxidant production. So I'm curious how it is that you  
25      assessed white cell function to make the statement. That's

1 the first question.

2 DR. HAYES: These were done at two sites, Dr.  
3 Weinblatt's and Dr. Moreland's sites, and basically for  
4 neutrophil function, these were classic ex vivo studies of  
5 the functionality of these cells. They were not given  
6 Enbrel or anything. All of the patients were on Enbrel at  
7 the time these samples were drawn to do this evaluation, so  
8 they had Enbrel on board when the samples were drawn.

9 DR. ABRAMSON: The second question has to do  
10 with the data on the numbers of people treated for 6 months  
11 and toxicities. We were told that there were 733 patients  
12 treated for 6 months, and I'm looking at page 100, and I'm  
13 curious about the people treated at the therapeutic dose  
14 for 6 months, which is 181 -- oh, I see, 181 is people  
15 treated at the therapeutic dose of 25 milligrams. I assume  
16 that 181 includes the 40-odd people in the 3-month study,  
17 the 16.0004. So I'm curious, how many actual people are we  
18 hearing about treated at the therapeutic 25-milligram dose  
19 for the 6-month observation period?

20 DR. HAYES: Can you add them up, Leslie?

21 We can add those up for you.

22 DR. ABRAMSON: Page 100 of your handout, in the  
23 right column.

24 DR. GARRISON: I don't have the handout here,  
25 but we will pull up the presentation slide showing the ICH

1 guidelines and how many patients were treated at various  
2 time intervals. Two hundred and thirty-nine patients in  
3 the open-label trial are included in that 6-month treatment  
4 period, and all of those patients received 25 milligrams of  
5 Enbrel subcutaneously twice weekly. We also had the 44  
6 patients in Protocol 16.0004 who then went on to long-term  
7 treatment at 25 milligrams, and we also had in the 16.0009  
8 trial the 78 patients who were treated with 25 milligrams  
9 of Enbrel. In addition to that, we've included here  
10 information from the blinded trial that is ongoing, where a  
11 third of those patients are on 10 milligrams, a third are  
12 on 25 milligrams, and a third are on placebo.

13 So the majority of the patients here -- I can't  
14 give you an exact number. I can probably in a few minutes.  
15 A majority of the patients here were treated with 25  
16 milligrams of Enbrel, and, of course, all of the prolonged  
17 experience that you're seeing here, the vast majority of  
18 those patients were treated with 25 milligrams of Enbrel.

19 DR. ABRAMSON: I think it would be important  
20 for us to get a real accurate number on that.

21 DR. GARRISON: I'll be able to do that in a  
22 second.

23 DR. PETRI: Dr. Frieri first, then Dr. Pucino.

24 DR. FRIERI: I had a question on the  
25 lymphoproliferative assay, why the strep enterotoxin was

1 chosen instead of staph aureus choanae, and why was maybe  
2 not EVB as another stimulator used in the assay.

3 DR. HAYES: The stimulators in these assays  
4 were actually chosen by the investigator at the University  
5 of Alabama who ran these studies for us, and it was his  
6 recommendation that this was what we did. We personally  
7 did not choose this. We deferred to his expertise in doing  
8 this.

9 DR. PETRI: Dr. Pucino?

10 DR. PUCINO: Was there a difference in the  
11 response for the patients that did not have any type of  
12 skin reaction at the site of injection?

13 DR. HAYES: Injection site reactions?

14 DR. PUCINO: Right. In other words, could this  
15 injection site reaction have affected a blind --

16 DR. HAYES: Can you pull that up?

17 No, we can actually show you that. It is R-5.  
18 This is the data at 3 months and 6 months for Study  
19 16.0009, showing patients who had injection site reactions  
20 and patients who had none, and R-6 shows the same data for  
21 Study 16.0014. So, no, there is no difference between the  
22 responses in those patients who had injection site  
23 reactions and those who did not.

24 DR. PETRI: Dr. Tilley first, then Dr. Yocum.

25 DR. TILLEY: I had a question of clarification

1 about your intention-to-treat analysis. Were your placebo  
2 patients followed until they dropped off of treatment, or  
3 were they all followed through the end of the study?

4 DR. HAYES: They were only followed until they  
5 dropped off therapy.

6 DR. TILLEY: So you don't have any data --  
7 that's why your person-years are so different between --

8 DR. HAYES: Yes, that's correct.

9 DR. PETRI: Dr. Yocum?

10 DR. YOCUM: Further commenting on the rashes,  
11 we spent a lot of time on the injection site reactions, but  
12 what about other rashes, as far as anaphylaxis, urticarial  
13 reactions? What was the breakdown in those?

14 And the second question relates to other  
15 cytokine inhibitors. Did you look at serum levels of IL-6  
16 to IL-1 beta? Did you look at other response modifiers  
17 that might give us some indication of the response?

18 DR. HAYES: Yes. While Dr. Garrison is looking  
19 -- or maybe she already has the first question. This is  
20 the adverse events in the controlled trials, grouped by  
21 rash and by urticaria, for the various dose groups. Here  
22 the dose groups are divided into patients who received on  
23 any trial less than 10 milligrams, so that's 16.0004 with  
24 the 0.25 and the 2 mg/m<sup>2</sup>, patients who received between 10  
25 and 25, so those are patients who received the 10

1 milligrams, or the few patients on 16 mg/m<sup>2</sup> who received  
2 less than 25, and then the largest group are obviously in  
3 the 25-milligram group. Shown here are the events per year  
4 comparing these events for the controlled trials.

5 DR. PETRI: Dr. Liang first.

6 DR. HAYES: You didn't get your second question  
7 answered.

8 DR. PETRI: I'm sorry. The IL-6 question,  
9 please.

10 DR. HAYES: If I could see G-3 --

11 DR. GARRISON: We did evaluate downstream  
12 effects of TNF inhibition. Forty-nine patients in the  
13 Phase III study were studied, and we found that, as seen  
14 with other TNF inhibitors, IL-6 was decreased, ICAM-1 was  
15 decreased, E-selectin was decreased, and MMP-3 was also  
16 decreased in the range of 10 to 20 percent relative to the  
17 placebo group.

18 DR. PETRI: Thank you.

19 Dr. Liang?

20 DR. LIANG: This was a beautiful presentation,  
21 and I'm sure there's an easy answer for this, and it's  
22 arithmetic. It's Slide 92, 98, and 105. If you look at  
23 the raw numbers, it looks like -- I don't know if this is  
24 going to be easy for you to respond to, because I'm talking  
25 off three different slides. On Slide 92, if you look at

1 the column "Enbrel and infection," that's 35 percent of  
2 349, that's about 122 patients. Is that correct? So I  
3 would assume that's the total of all infections. Am I  
4 right about that?

5 DR. GARRISON: Slide 92 is for all controlled  
6 studies.

7 DR. LIANG: Okay. All controlled studies, so  
8 the total of infections in all those is about 122, right?

9 DR. HAYES: Close.

10 DR. LIANG: Well, anyway, and then if you fast  
11 forward to 98, that says that these are the URI type or the  
12 minor infections, and there are about -- if you add these  
13 up -- maybe that's where I did it wrong. These are  
14 percents, I guess.

15 DR. HAYES: Yes.

16 DR. LIANG: Oh, I see. So you're going to  
17 assure me, then, that the numbers that represent -- and  
18 these percentages -- when you add them to the medically  
19 important infections, which is numbers, not percents, and  
20 it's events, not individuals necessarily, that that will  
21 add up to 122? Otherwise, there are some missing bodies  
22 here.

23 DR. HAYES: I'm sure Dr. Garrison will assure  
24 you that her numbers are correct, or at least our  
25 statistician will assure you our numbers are correct.

1 DR. LIANG: All right. It's just confusing  
2 when you go back from percents into real numbers.

3 DR. HAYES: Yes.

4 DR. LIANG: Okay.

5 DR. HAYES: We can look and make sure, but --

6 DR. PETRI: Dr. Silverman first, then Dr.  
7 Katona.

8 DR. SILVERMAN: Very similar to Dr. Liang's  
9 question, I had difficulties with Slide 33 and 34, where we  
10 look at, as an example, changes in the CRP in the placebo  
11 group, where it shows it went from 3.8 to 3.8, the mean  
12 value, yet we see a -170 as a percentage change. It may be  
13 my ignorance of statistics, but can somebody explain how  
14 that's possible? And it occurs many times.

15 DR. HAYES: Mary?

16 This is Mary Lang, who is the statistician  
17 responsible for the study.

18 DR. LANG: One of the things that happens with  
19 the CRP is that the values can range from about 0.8 up to  
20 about 6 or so, and so when subjects have a very -- subjects  
21 can have dramatic percent changes from their baseline  
22 levels. If they start at 6 and then normalize down to  
23 under 1, that is a six-fold change in the percentage. So  
24 that's how the placebo group could have actually a  
25 worsening in their CRP, and they might start near the

1 normal range and then have a six-fold worsening up to a  
2 value of, say, 6 or so, resulting in an average change for  
3 the group, a large drop for the group.

4 DR. SILVERMAN: So maybe it was just my  
5 interpretation. So the mean is the mean percentage of the  
6 changes.

7 DR. LANG: Yes, that's right.

8 DR. SILVERMAN: Rather than the 3.8. So it's  
9 just a different way or a more convincing way or a better  
10 way, whatever.

11 DR. LANG: That's right. When we looked at the  
12 medians, they were not nearly so wildly erratic.

13 DR. SILVERMAN: Which brings me to my second  
14 question, and that was, in the briefing document, if you  
15 look on -- for Protocol 16.0009, we have most patients  
16 finishing a trial, yet the median time on trial is not 6  
17 months, it's 5.9, and that occurs many times. Again, I  
18 understood median to mean what the 50 percent person was  
19 at. Now, I don't understand how over 90 percent could  
20 finish a trial, yet the median being 5.9.

21 DR. LANG: That, I believe, is due to a few  
22 subjects coming in early for their visits, so some of the  
23 visits were conducted maybe up to a week earlier or so,  
24 resulting in the 5.9.

25 DR. SILVERMAN: But that would be a lot, right?

1 Fifty percent of the patients were 5.9, implying most  
2 patients came in early.

3 DR. LANG: Yes.

4 DR. PETRI: Dr. Katona?

5 DR. KATONA: My first question relates to the  
6 slide, Dr. Garrison, on immunocompetence. You showed us  
7 some data indicating that the quantitative immunoglobulins  
8 were normal on patients receiving the drug. I'm looking at  
9 things from a special pediatric point of view, and for us  
10 it's extremely important that not only the total  
11 immunoglobulins, but the specific responses to certain  
12 antigens and especially to immunizations are going to be  
13 normal. Have you evaluated anything like a Pneumovax  
14 vaccine on the adults or anything that you would have some  
15 data about specific immune responses?

16 DR. HAYES: We have not done that to this  
17 point. We do have a significant number of adult patients  
18 who did receive flu vaccines, some who received Pneumovax,  
19 et cetera. This was not prohibited by the protocol. But  
20 we have not done evaluations to see what their responses  
21 were, and, therefore, I can't answer your question.

22 DR. KATONA: My second question, if I may have  
23 a second question --

24 DR. PETRI: Please.

25 DR. KATONA: Again, going back to the most

1 common side effect, the local reaction, the Grade 1 and 2  
2 reactions, about what time did they start, how long did  
3 they last, and in a practical aspect, does this indicate  
4 that the drug has to be given in a physician's office, or  
5 is that something that the patients can take home and  
6 administer themselves? Some of us on the practical side,  
7 if you could fill us in, please.

8 DR. HAYES: I will answer from our point of  
9 view, and then maybe Dr. Weinblatt, as a treating  
10 physician, could respond to your question, too.

11 This therapy was delivered as an outpatient  
12 therapy, with patients delivering their own drug at home,  
13 and these reactions tend to be short-lived, lasting maybe 2  
14 to 4 days, they're all mild, they do not interfere in any  
15 way with the patient's activity or ability to inject.  
16 Patients are instructed to inject at different sites on a  
17 rotating basis so they don't inject in the same site all  
18 the time.

19 Dr. Weinblatt, would you care to comment on  
20 your patients' reactions?

21 DR. WEINBLATT: Like any subcutaneous therapy,  
22 there is a patient education program that's required. This  
23 is using a small-needle syringe, an insulin syringe with  
24 generally a 27- or 28-gauge needle. Most patients can be  
25 educated in a 30-minute session. They're frequently shown

1 a film about self-injection, and I would say the vast  
2 majority of our patients can successfully inject  
3 themselves. There's no issue regarding anaphylaxis, so  
4 there's no reason for them to have to inject in an observed  
5 setting.

6 As Dr. Hayes mentioned, in our experience --  
7 and I think Dr. Moreland's and Dr. Paulus' experience would  
8 be similar -- the reaction occurs at the site of injection  
9 generally within 24 hours of the injection, and by the time  
10 they go to inject the other side, which is generally their  
11 contralateral thigh, the injection site reaction on their  
12 initial side is already resolving. Our patients, at least,  
13 will report that they'll inject one side, they'll start to  
14 see maybe redness or perhaps pruritus, rarely tenderness,  
15 and by the time they go to inject the other side, the  
16 initial side is already improving.

17 Our experience has been over time that this  
18 actually improves. There are some patients that have a  
19 chronic reaction, but it's very minimal, and we didn't have  
20 any patients in our trial that discontinued at our site due  
21 to this issue.

22 DR. HAYES: I think it needs to be remembered,  
23 too, as Dr. Garrison pointed out, half the patients don't  
24 even have injection site reactions, and of those that do,  
25 the vast majority have less than five in the entire course

1 of their therapy. So it's a relatively infrequent event  
2 for the majority of patients.

3 DR. PETRI: Thank you.

4 Dr. Hess, followed by Dr. Luthra, then Dr.  
5 Brandt.

6 DR. HESS: Just a few quick questions. One, I  
7 think I heard you say that one patient going into the study  
8 had lupus. I'd be interested to know what happened to the  
9 lupus.

10 DR. HAYES: This was a patient who, I guess,  
11 had what rheumatologists call "rupus," as a non-  
12 rheumatologist, but this was a patient who had a history of  
13 systemic lupus, at the time of entry into the trial was  
14 rheumatoid factor-positive, and met the criteria. This  
15 patient had a persistently positive double-stranded DNA and  
16 crithidia throughout the trial. She had no recrudescence  
17 of her symptoms of her lupus.

18 DR. HESS: And the second question is really a  
19 clarification on your cancer, on the six patients who had  
20 the cancers. I think that was the slide in which that was  
21 the 6-month trial. It seems a lot of cancers to be  
22 uncovered in that period of time. What kind of a pre-  
23 workup, overall health workup, did these patients have?

24 DR. HAYES: No, these cancers did not occur --  
25 the controlled trials were either 3 or 6 months, but all of

1 these patients continued on long-term therapy, and this is  
2 actually the cancers seen in following these patients out  
3 over a total of 733 patient-years, with patients out to 2  
4 years. This is not just the 6-month block. As a matter of  
5 fact, we have the slide that shows you when these occurred.  
6 They occurred throughout the entire time.

7 DR. HESS: But the total number of patients  
8 followed for the 2 years is actually very small. Can you  
9 just clarify that? Are you actually following all of the  
10 patients?

11 DR. HAYES: Yes. We're not following placebo  
12 patients who dropped out and have not chosen to come back  
13 into our trial.

14 DR. HESS: But that's a substantial number.

15 DR. HAYES: No, most of our placebo patients  
16 have actually chosen to enter our long-term trial.

17 Maybe Dr. Ely, who is here from the SEER  
18 database and has reviewed our data, could comment on this.

19 DR. ELY: The predicted numbers of cancers for  
20 these cases was done by looking at what we would expect in  
21 the regular population of the United States for the number  
22 of person-years that these people were followed, and there  
23 are a significant number of patient-years. Even though  
24 most are followed to 2 years, there's quite a history now  
25 of these patients. So using the expected rates of cancer

1 for people of this age, we were able to use incidence rates  
2 from the U.S. population to predict the number of cancers  
3 we would have seen over this amount of time, and that was  
4 seven, and that's exactly how many cancers were seen.  
5 There are fewer person-years in the placebo group, because  
6 they weren't followed as long. One cancer about was  
7 expected, and one cancer was seen. For the increased  
8 number of patient-years of observation in the treatment  
9 group, about seven cancers were expected, and about seven  
10 cancers were seen.

11 DR. PETRI: Thank you.

12 Dr. Luthra, followed by Dr. Brandt, followed by  
13 Dr. Callahan, and then Dr. Simon.

14 Dr. Luthra?

15 DR. LUTHRA: I had a quick question. Do you  
16 have any experience with a dose of more than 25 milligrams  
17 a day?

18 DR. HAYES: No, we do not. Twenty-five  
19 milligrams twice a week is the highest dose that we have  
20 tested in this patient population.

21 DR. LUTHRA: How did you decide on that dose?  
22 Do you have any information on that?

23 DR. HAYES: The original randomized trial was  
24 done over the range of 0.25 to 16 mg/m<sup>2</sup>, and the responses  
25 seen at 16 mg/m<sup>2</sup> were pretty dramatic. So when we moved

1 into the next randomized trial, we decided for patient ease  
2 to move to a flat dose rather than patients having to  
3 manipulate syringes, et cetera, and chose 25 milligrams as  
4 a dose that would be approximately equivalent to 16 mg/m<sup>2</sup>  
5 and went with that dose.

6 DR. PETRI: Dr. Brandt?

7 DR. BRANDT: This has been, I think, a very  
8 nice presentation. You've said nothing, though, about  
9 radiography, and you've had an opportunity to follow, as  
10 you've said, a number of patients for 6 months and longer,  
11 and sometimes considerably longer. I presume you're  
12 gathering such data. Is there anything you can tell us  
13 about that with regard to erosion accumulation?

14 DR. HAYES: Patients entered into the trials  
15 for which you are seeing data today have not had serial X-  
16 rays done. We have ongoing and currently accrued a study  
17 in early rheumatoid arthritis, in which we are comparing  
18 Enbrel with methotrexate in a placebo, double-sham, blinded  
19 trial, in which one of the primary endpoints is  
20 radiographic evidence of disease. So we do not have data  
21 to present today for you.

22 DR. PETRI: Dr. Callahan?

23 DR. CALLAHAN: Just to follow up a little bit  
24 on Dr. Brandt's question, in your long-term -- and then I  
25 have some other questions, but in your long-term following,

1 are there any measures of damage being looked at in long-  
2 term, or is it all just safety measures?

3 DR. HAYES: Correct me if I'm wrong, Leslie,  
4 but in the patients who are coming off the trials you are  
5 seeing today, they are only being followed for safety and  
6 clinical efficacy. The patients who will be coming off of  
7 our 16.0012 trial, which is the large disease modification  
8 trial, as they move into their long-term study, they will  
9 continue to have serial radiographic evaluation and studies  
10 done.

11 DR. CALLAHAN: And that will be the measure of  
12 damage?

13 DR. HAYES: Yes.

14 DR. CALLAHAN: In terms of the HAQ disability  
15 index, was the 20-item disability index used in all three  
16 studies? And if so, why is there a different scoring  
17 mechanism used in 16.0004?

18 DR. HAYES: Dr. Garrison?

19 DR. GARRISON: The 20-item disability index was  
20 used in 16.0009 and in 16.0014. In 16.0004 a slightly  
21 modified version of the HAQ was used, and that's why we've  
22 focused our analysis on the 16.0009 and 16.0014 data.  
23 We've also analyzed the 16.0004 HAQ disability index, as  
24 you can see, in a slightly different manner, I think  
25 reflecting at that point the lack of consultant input from

1 quality of life and health-related outcome personnel at  
2 that stage of our development of TNF receptor.

3 DR. CALLAHAN: Okay. And could you clarify  
4 what the scales are in the HAQ? Because I don't know the  
5 published scales of the vitality and mental health in the  
6 HAQ.

7 DR. GARRISON: The HAQ that we used was the  
8 Stanford HAQ from 1996. I think it's called Phase 30. In  
9 that HAQ there is included the entire set of questions from  
10 the mental health as well as the vitality domains of the  
11 SF-36.

12 DR. CALLAHAN: For just those subscales.

13 DR. GARRISON: Yes, just those subscales were  
14 included.

15 DR. CALLAHAN: And then my last question is,  
16 given this patient education component of the home  
17 injection, what was the mean formal education level of the  
18 study population?

19 DR. HAYES: We did not collect that data. I  
20 think that maybe our consultants could again say whether or  
21 not this was difficult. I think Dr. Weinblatt said  
22 approximately 30 minutes to teach most patients. We did  
23 not collect that kind of data.

24 DR. PETRI: Dr. Simon, then Dr. White.

25 DR. SIMON: I have three questions, two to the

1 presenters of this very nice presentation and one to CBER.  
2 The first is, I'd like further definition of how you define  
3 lack of efficacy and the "other," and if you can just  
4 review that for me, what the criteria are exactly in these  
5 that meant lack of efficacy and what you meant by "other."  
6 That's one.

7 DR. HAYES: We actually have a definition on a  
8 slide. The definition of lack of efficacy, "Patient had to  
9 receive at least a 2-week minimum. If they had progression  
10 during that 2 weeks, then they could come off, and four of  
11 the following criteria had to be met to qualify for  
12 progression of disease." So it was defined as to what the  
13 patient should have for progression of disease.

14 DR. SIMON: And what was the "other" component  
15 for dropout besides lack of efficacy? You just identified  
16 it as "other." Could you define what those were?

17 DR. HAYES: Do we have those on a slide,  
18 Leslie? Do you want to discuss that? Because I'm not as  
19 familiar with the data as you are.

20 DR. GARRISON: There was a whole variety of  
21 reasons. Some patients decided that they didn't want to  
22 participate in a clinical trial anymore, they didn't like  
23 coming in every month for evaluations. Other patients  
24 moved away. Any event that could be considered an adverse  
25 event was coded as an adverse event. If the patient said

1 that they didn't like the potential for having a rash or an  
2 injection site reaction, then those patients were  
3 classified as "other," because they did not actually have  
4 this event, but any patient who said that they did not want  
5 to continue because they did not like having an injection  
6 site reaction or having a headache, even though the  
7 physician themselves were not calling those things adverse  
8 events, we classified those as adverse events. So the  
9 "other" was a mishmash of various things.

10 DR. SIMON: Okay. And before you sit down,  
11 because I think you're best capable of answering this  
12 question, Dr. Petri had asked about the GPL units for the  
13 anticardiolipin antibody, and you presented data that  
14 demonstrated differences of change with therapy and without  
15 therapy, et cetera. But I wondered whether or not -- you  
16 only showed data expressed as greater than or equal to 23  
17 GPL units. Could you actually tell us what the spread of  
18 level was, how high were the levels, and were there  
19 differences in levels between the placebo and patients that  
20 were treated, or was there a dose response issue here?

21 DR. GARRISON: There was no dose response issue.  
22 at all, and I don't have that graph in front of me, but I  
23 think that in the briefing document for the FDA, you've  
24 seen the spread of the double-stranded DNA and how they  
25 sort of just zigzag around, and that's the same kind of

1 thing that we were seeing with the anticardiolipin IgG,  
2 IgM, ANA. All of those things -- there were only a few  
3 patients who were consistently elevated, the patient we've  
4 discussed before who had preexisting lupus, and there was  
5 one placebo patient, as you could see, who was consistently  
6 elevated. But most of the other patients were just --

7 DR. SIMON: And it was 6-month data, not longer  
8 than that. Is that right?

9 DR. GARRISON: Not longer than that. We do  
10 have some additional data on patients in the long-term  
11 treatment trials where we collected samples after the 6-  
12 month time point, and the same pattern is seen there. Most  
13 of the time these patients are negative, there is no  
14 consistent pattern of elevation. Again, there's  
15 variability in these assays that I think are manifested by  
16 performing these tests serially with different lots.

17 DR. SIMON: Okay. Thank you.

18 My final question is actually to the people at  
19 CBER. Those of us who have been on this committee for a  
20 while have been taught to look for two times the upper  
21 limit of the dose used in drugs, from a safety point of  
22 view and PK/PD point of view. In treating or using  
23 biologic agents, since the dose that's been chosen is the  
24 16 mg/m<sup>2</sup>, or the highest dose, and we see no data at a  
25 higher level, is that same rule, that same concept not

1 applicable in biologic therapies?

2 DR. JEFF SIEGEL: I can't comment specifically  
3 on whether we have a standard of testing at 2x dose, but we  
4 did note in our review of the data that there's no plateau  
5 of efficacy, so it's possible that exploration of higher  
6 doses would be something that would be helpful, and we'd  
7 like, certainly, the committee's comments on that.

8 Regarding the safety, I'll let you comment on  
9 that.

10 DR. JAY SIEGEL: No, I just wanted to comment  
11 more broadly on what usually happens with biologics, since  
12 that was asked. I would say that it's generally the case,  
13 certainly more often than not and certainly preferable and  
14 advisable, that there be dose ranging where considered  
15 appropriately safe and some exploration of doses higher  
16 than the dose ultimately studied in Phase III. However, we  
17 don't have any rule or standard to that effect, so having  
18 determined this dose to be the best dose that was studied  
19 in Phase II, proceeding to Phase III trials with it would  
20 certainly be within what would be considered an acceptable  
21 method of dose development. However, certainly as the  
22 discussion proceeds, we would be interested in the  
23 committee's input as to whether higher doses ought to be  
24 explored.

25 DR. PETRI: Thank you.

1 Dr. White?

2 DR. WHITE: I have two questions. Of the six  
3 patients who had anti-Enbrel antibodies, did any of those  
4 have IgE anti-Enbrel antibodies?

5 DR. HAYES: This was not measured.

6 DR. WHITE: Have any patients stopped Enbrel  
7 for a period of time, then restarted it, and had any sort  
8 of urticarial kinds of events?

9 DR. HAYES: As Dr. Garrison indicated, all of  
10 the patients on our first randomized trial, 16.0004, and  
11 also on our Phase I trial, 16.0002, were offered the  
12 opportunity to come onto a long-term safety trial, which is  
13 designated 16.0008, and those patients came from all  
14 groups, from the placebo group, from the low-dose group,  
15 the median-dose group, and the high-dose group. Those  
16 patients came back into that study. They had similar  
17 efficacy responses, they had no allergic phenomenon, no  
18 increased incidence of injection site reactions, no  
19 increased incidence of rashes.

20 DR. WHITE: Had they been off it for some  
21 period of time?

22 DR. HAYES: They had been off for a median of  
23 18 months.

24 DR. WHITE: Okay, great. That's very helpful  
25 to me. The next question actually has to do with flares

1 after the drug is stopped. Could you please tell us what  
2 you know, numbers of patients, numbers of flares, response  
3 when they're put back on drug? What do you all know about  
4 this?

5 DR. HAYES: Leslie, if you could put back up  
6 the joint slide for 16.0004, these patients did not flare  
7 in the sense that they had rapid, horrible disease above  
8 baseline. As the slide that Dr. Garrison's going to show  
9 you shows, there was just a gradual increase over 2 to 6  
10 weeks of increasing activity of their disease. None of  
11 these patients flared up beyond baseline. They just  
12 gradually came back up toward their baseline levels, and  
13 then, obviously, when this happened, if they were having a  
14 problem, many of them went back on other therapy, because  
15 at that time we had no long-term trial. But there was not  
16 a rebound flare phenomenon in any of these patients.

17 DR. WHITE: And as you offered long-term open-  
18 label therapy to these patients, they have again appeared  
19 to respond, if I understand what you've told me?

20 DR. HAYES: Yes, they have. We actually have  
21 some slides to show this. The patients who were on the 16  
22 mg/m<sup>2</sup> of Enbrel in this trial and went onto the flat dose  
23 of 25 had almost identical responses as to what they had  
24 before. Patients who had received the very low dose of  
25 Enbrel in previous trials had a response that was more

1 similar to the 25-milligram slide. This slide shows the  
2 patients who were retreated, who had been on 16 mg/m<sup>2</sup> and  
3 went to 25. The dotted lines are when they were on 16.0004  
4 and 16 mg/m<sup>2</sup>, and the solid lines are when they came to  
5 16.0008 and received 25, and, again, a median interruption  
6 of therapy of 18 months.

7 DR. PETRI: Dr. Harris, but Dr. Harris'  
8 question will be the last one before the break.

9 DR. HARRIS: And it may be an easy one.

10 I need to be convinced again and just to review  
11 with respect to the response of patients to infection when  
12 they're on this drug, particularly serious infections. Do  
13 you have enough data to say with confidence that being on  
14 this drug would not in some way affect their response to  
15 infection?

16 DR. HAYES: You have in the back of the  
17 briefing document from Immunex the actual case histories of  
18 every one of these patients, and if you look at these  
19 patients, of the 22 infections in 20 patients, 15 of the  
20 patients never interrupted their Enbrel during their entire  
21 treatment of their infection, and their infections resolved  
22 without incident. The other patients who did have  
23 interruptions, there were patients who had one or two doses  
24 interrupted, other patients had their therapy discontinued  
25 for longer periods of time.

1                   We feel that these patients had a pretty  
2 typical course of infection in this situation, and maybe  
3 later after the break, if there are more questions, Dr. Jim  
4 Lui from California is here with us today, who has reviewed  
5 all of these patients and could discuss this with you. But  
6 we feel their course of infection is relatively as would be  
7 expected for this patient population.

8                   DR. PETRI: I'm actually going to ask committee  
9 members who have additional questions of clarification to  
10 let me know during the break so that I can plan the time,  
11 and Bill Freas has an announcement before the break.

12                   DR. FREAS: For safety reasons, we're required  
13 to keep a walkway down the center of the room and around  
14 the edges of the room. If you have moved a chair into one  
15 of the walkways, would you please return it to its original  
16 position before the break. Thank you for your cooperation.

17                   DR. PETRI: So we'll break now until 10:30.

18                   (Recess.)

19                   DR. PETRI: Dr. Liang has the first question,  
20 followed by Dr. Katona, and at that point we will move to  
21 the FDA presentation.

22                   Dr. Liang?

23                   DR. LIANG: Well, I just wanted to follow up on  
24 Dr. White's concern about stopping and flares.

25                   DR. PETRI: Excuse me a minute. I need to have

1 the audience be completely quiet out of respect to Dr.  
2 Liang.

3 Dr. Liang?

4 DR. LIANG: No one has ever done that before.

5 (Laughter.)

6 DR. LIANG: I'm used to hecklers.

7 But, anyway, I just wanted to follow up on Dr.  
8 White's question about flares after stopping the injection,  
9 and I think your own data suggest that that happens,  
10 because that's the higher dose which is your recommended  
11 dose. The graphic display of particularly the joint  
12 swelling is obviously increased after you stop.

13 DR. HAYES: Maybe it's the semantic use of what  
14 I'm talking about as a flare and the usual flare of  
15 rheumatology. What I was trying to convey is that we  
16 didn't have patients who had just rapidly progressive  
17 disease out beyond baseline, although they did have disease  
18 come back toward baseline.

19 DR. LIANG: But show that slide. I think if  
20 you look in the swollen joints, the yellow line is what we  
21 feel, as rheumatologists, is a flare. I just want to say  
22 that's -- I don't know how you're calling it, but visually  
23 that's what we mean.

24 DR. HAYES: I guess we're talking about they  
25 start at baseline at 25 and --

1 DR. LIANG: I know, but you've got them down to  
2 that point, and within a month they're almost halfway back  
3 to their original --

4 DR. HAYES: Yes. Okay.

5 DR. PETRI: Dr. Katona?

6 DR. KATONA: We have not heard any detailed  
7 presentation on the pediatric data, and there is one aspect  
8 that I would be very interested in, and just for background  
9 information, in children pharmacokinetics of many drugs are  
10 very different than in adults. Most of the time, usually  
11 the children have a better clearance. Do you have any data  
12 on children on the pharmacokinetics of Enbrel?

13 DR. HAYES: Yes, we do. We do have  
14 pharmacokinetics.

15 Joan, do you want to go ahead and show that  
16 data?

17 This is Dr. Joan Bradley, who's a  
18 pharmacokineticist from Wyeth-Ayerst, who has been working  
19 with us.

20 DR. BRADLEY: As part of the study of children  
21 with JRA, plasma concentrations were collected throughout  
22 the study, and if I could have Slide K-31, please, you'll  
23 remember this morning Dr. Seamon showed concentrations  
24 measured over the study, and here we show the children's  
25 concentrations. The averages are somewhat lower, but still

1 overlapping what's observed in adults. These children were  
2 dosed at a rate of 0.4 milligrams per kg.

3 DR. PETRI: Thank you.

4 We are now going to move to the FDA  
5 presentation from the Center for Biologics Evaluation and  
6 Research, and I'd like to introduce Dr. Jeffrey Siegel from  
7 the Division of Clinical Trial Design and Analysis.

8 DR. JEFF SIEGEL: Good morning, and thank you.  
9 I will be discussing the clinical aspects of the biologic  
10 license application for Enbrel for rheumatoid arthritis.

11 To begin, I'd like to just review the sponsor's  
12 proposed indication for Enbrel. In their application, they  
13 propose that "Enbrel is indicated for the treatment of  
14 patients with active rheumatoid arthritis. Enbrel  
15 significantly decreases disease activity, increases  
16 functional ability, and improves quality of life. Enbrel  
17 is also effective in combination with methotrexate  
18 therapy." I'd just like to point out here that this  
19 proposed indication doesn't state anything about limiting  
20 the patient population with regard to severity of disease  
21 and failure of prior DMARDs.

22 What I would like to begin with is a review of  
23 the efficacy data. I'll be covering the design of the  
24 Phase III pivotal trial, then move on to the endpoint  
25 analysis, and then provide a variety of corroborating

1 analyses. Then I'll go on and review the safety data, and  
2 then I'll talk about the pediatric data from the juvenile  
3 rheumatoid arthritis trial, and then Dr. David Green will  
4 review the pharmacokinetic data.

5 Three randomized, controlled trials were  
6 submitted in support of efficacy of Enbrel in rheumatoid  
7 arthritis. I'll be beginning with the Phase III trial, and  
8 then talk briefly about the Phase II trial, and then talk  
9 about the methotrexate combination trial.

10 The design of the Phase III trial, as you heard  
11 earlier from the sponsor, was as a randomized, controlled  
12 trial of two dose levels of Enbrel, 10 milligrams and 25  
13 milligrams, versus placebo, given subcutaneously twice  
14 weekly for 6 months. The trial allowed concomitant  
15 medications of low-dose NSAIDs, up to 10 milligrams of  
16 prednisone or its equivalent, and low-dose corticosteroids  
17 as well as low-dose non-steroidals. For patients who were  
18 previously on a disease-modifying antirheumatic agent, a  
19 DMARD, a washout phase of at least 4 weeks was required  
20 before randomization.

21 The primary endpoint in the trial was the ACR  
22 20 response, which Immunex defined for you earlier, at the  
23 3-month time point. In the Phase II trial, it was  
24 determined that there was an increased proportion of  
25 patients who dropped out early due to lack of efficacy, and

1 there were some concerns about unblinding. For this reason  
2 and for others, independent blinded joint assessors were  
3 recruited to do all the joint assessments for the primary  
4 endpoint to decrease the subjectivity of this analysis.

5 The inclusion criteria for this trial, as for  
6 the others that I'll be reviewing, is active rheumatoid  
7 arthritis in subjects who failed one to four DMARDs.

8 As I mentioned before, there was an increase in  
9 the proportion of subjects in the Phase II trial who  
10 dropped out early due to lack of efficacy. Because  
11 dropouts may end up being missing data in the final  
12 analysis, it was decided that subjects who dropped out  
13 early, that there should be an early escape clause for lack  
14 of efficacy, and this was prespecified in the protocol, and  
15 I will just briefly mention the criteria, since they were  
16 mentioned by Immunex earlier.

17 Subjects who decided to drop out due to lack of  
18 efficacy to meet protocol prespecified criteria for failure  
19 of therapy should be on study agent for at least 2 weeks  
20 with inadequate control, have no improvement in physician  
21 or patient global assessment or a worsening compared to the  
22 best value, less than a 10 percent improvement in tender  
23 joint count or swollen joint count or a 20 percent  
24 improvement compared to the best value during the studies,  
25 a tender joint count of at least 12, a swollen joint count

1 of at least 10, and these levels of arthritis would require  
2 a change in antirheumatic therapy.

3 I'd like to go over a little bit the patient  
4 disposition, and the numbers differ just a little bit from  
5 what Immunex presented to you, for reasons that I'll  
6 present. Two hundred and forty-six patients were  
7 randomized into the trial, and the subjects randomized are  
8 shown in the first line. Some patients did not receive any  
9 dose at the beginning of the trial. This was apparently  
10 due to subjects who did not meet inclusion criteria, who  
11 were never dosed. This was less of a problem later on in  
12 the trial. But the numbers who received one dose were the  
13 modified intent-to-treat population, and this is a  
14 population that was the population for analysis  
15 prespecified in the protocol.

16 On the next line, you can see the percent of  
17 subjects who completed the first 12 weeks, or 3 months, of  
18 therapy, and you can see that fewer patients in the placebo  
19 arm completed 3 months of therapy compared to the subjects  
20 in the two Enbrel doses. The reasons for failure to  
21 complete the first 3 months of therapy are shown in the  
22 last three lines. Thirty-five patients in the placebo arm  
23 dropped out early due to protocol prespecified lack of  
24 efficacy. Nine patients in the low-dose and eight patients  
25 in the 25-dose group dropped out early due to protocol

1 prespecified lack of efficacy. The next line shows the  
2 patients who dropped out due to toxicity -- one in placebo,  
3 three each in the two Enbrel arms -- and the last line  
4 shows the subjects who dropped out for other reasons. This  
5 included protocol violations, patients who just elected to  
6 drop out. I'll go into more detail why the patients  
7 dropped out due to safety later on in my presentation.

8           The top line just shows the data I've already  
9 shown you for the subjects who completed 12 weeks. The  
10 next line shows you the small number of additional patients  
11 who dropped out between 3 months and 6 months during the  
12 trial, and the reasons for dropout during that period are  
13 shown in the last two lines. Seven dropped out due to lack  
14 of efficacy meeting protocol prespecified criteria in the  
15 placebo group compared to five in the low-dose and four in  
16 the high-dose Enbrel arms, and the last line shows the  
17 small number of patients who dropped out for other reasons.

18           This slide shows you the demographics. I won't  
19 go through this in detail because you already saw this data  
20 from Immunex, but I do want to point out that this  
21 population had long duration of rheumatoid arthritis,  
22 around 12 years in all the groups, and this and other  
23 parameters shown here were reasonably well balanced between  
24 the different arms. Approximately 80 percent of the  
25 subjects were positive for rheumatoid factor.

1                   Approximately 90 percent of the subjects had  
2 previously been treated with methotrexate, and the mean  
3 number of DMARDs that the patients had been on in the past  
4 was approximately three and was similar between the  
5 different arms. Approximately 45 percent of patients were  
6 on any DMARD at the washout. In the last two lines, I show  
7 you the baseline concomitant therapy that the patients were  
8 receiving, and there are some imbalances here that I want  
9 to point out. First, somewhat more patients, 81 percent,  
10 were on baseline concomitant corticosteroids in the high-  
11 dose Enbrel group, higher than seen in placebo. The  
12 proportion of patients on NSAIDs at baseline and throughout  
13 the trial was somewhat higher in the placebo group compared  
14 to the two Enbrel dose groups, and I'll talk about this  
15 more later.

16                   The arthritis activity at baseline was also  
17 covered earlier by Immunex. Suffice it to say that these  
18 patients had very active rheumatoid arthritis, with around  
19 33 tender joints and around 25 swollen joints, high levels  
20 of disease activity with regard to patient and physician  
21 global assessment, pain, and functional disability, as well  
22 as increases in acute phase reactants.

23                   I want to just go into a little bit of detail  
24 on what questions were included in the health assessment  
25 questionnaire, although Immunex covered this earlier on

1 this morning. The health assessment questionnaire that was  
2 used in this trial was a six-page patient-administered test  
3 of the effect of their illness on the patient's functions  
4 in daily life activities. The questions assess the degree  
5 of difficulty patients experience with performing life  
6 activities, including dressing, eating, and walking. It  
7 includes questions on the need for help from another person  
8 for activities of daily living, questions on change in  
9 physical limitations over a 6-month time frame, the amount  
10 of pain, joint tenderness and swelling, and their effect on  
11 activities and social functioning. There were also  
12 questions on overall health status, energy, and happiness,  
13 considered over the past 4-week time frame.

14 This shows the responses, both the primary  
15 endpoint and the secondary endpoint prespecified in the  
16 protocol. I won't go through this in detail, because  
17 you've already seen these data from Immunex, but I would  
18 just like to point out that there were significantly  
19 increased proportions of subjects with ACR 20 responses at  
20 3 months in the Enbrel group compared to placebo, and this  
21 was the protocol prespecified primary endpoint. In  
22 addition, there were increased proportions of patients  
23 achieving an ACR 20 at 6 months and ACR 50 responses at 3  
24 months and at 6 months.

25 I'd like to also point out that there are

1 statistically significant differences between the  
2 proportion of patients achieving ACR 20 response at 3  
3 months in the 25-milligram dose group compared to the  
4 lower-dose group, and this was also seen in the ACR 50  
5 responses at both time points.

6 One other point to make is that the proportion  
7 of patients responding in the high-dose group is higher  
8 than in the low-dose group, and this is especially marked  
9 in the ACR 50 assessment. This suggests a lack of plateau  
10 in dosing, which we can perhaps discuss more later.

11 This slide shows the components of the ACR 20,  
12 and I didn't go through what these components are before,  
13 but they're shown here. This data, unlike the data you saw  
14 before, are the median responses, and I chose this because  
15 of the problems that were pointed out by Dr. Silverman that  
16 you end up with very large worsening in the CRP. When the  
17 data were examined, it was found that there was a great  
18 deal of skewing, and a small number of patients with large  
19 increases skewed the data, so it was decided that median  
20 percent improvement might be a better measure of central  
21 tendency. As you can see here, there was a larger degree  
22 of median percent improvement in all of the measures,  
23 including both measures of joint counts, the patient's pain  
24 assessment, the patient/physician global assessment, as  
25 well as in both measures of acute phase reactants.

1           The FDA performed an additional analysis of  
2 efficacy. This test is called the Smirnov test, and two  
3 features that it has that differ from the test that you've  
4 seen before are that it categorizes patients not just into  
5 whether they responded or did not respond, but additionally  
6 categorizes them based on the degree of response that they  
7 had. So for each arm of the study, you see the proportion  
8 of patients who had no response, the proportion of patients  
9 who had an ACR 20 percent response or better, the  
10 proportion with an ACR 50 percent response or greater, ACR  
11 70 percent response or greater. In addition, this test,  
12 unlike some other statistical tests, does not make any  
13 assumptions about normality of the data.

14           What you can see is that an increased  
15 proportion of subjects in the 25-milligram and 10-milligram  
16 arm had responses compared to placebo. This was  
17 significant both in the comparison of placebo with the  
18 high-dose Enbrel group, as well as significant in the  
19 comparison between the low-dose and high-dose Enbrel  
20 groups.

21           You've already seen the disability index data  
22 based on the health assessment questionnaire. The baseline  
23 measure was balanced in the three groups, 1.6 and 1.7, and  
24 there was a decrease seen at Month 3 and Month 6 in both  
25 Enbrel-treated groups, and the percent improvement is shown

1 at the bottom here, 36 percent and 39 percent at 3 and 6  
2 months, respectively, compared to 8 percent and 2 percent  
3 in the placebo group.

4 I'm presenting on this slide several  
5 exploratory post hoc analyses of the functional data based  
6 on the health assessment questionnaire. At an earlier  
7 meeting of the Arthritis Advisory Committee, a question was  
8 asked about subjects who had large degrees of improvement  
9 in their HAQ in the study versus just comparing mean data  
10 across all patients. What's shown here are the proportion  
11 of all subjects who achieved improvement in their HAQ of  
12 one unit or greater, and I want to remind you that the HAQ  
13 is a 0 to 3 scale, so not all patients could achieve this.  
14 Certainly, anyone with below a 1, any of those patients  
15 could not. But I'm showing you the proportion of patients  
16 who did achieve a unit of one or greater decrease in their  
17 HAQ. You can see that at 3 months, 21 percent of Enbrel  
18 25-milligram subjects achieved this level of improvement  
19 versus 3 percent in placebo. At 6 months, 15 percent of  
20 Enbrel-treated patients achieved this, whereas 1 percent of  
21 placebo patients had.

22 Two other exploratory analyses were presented  
23 earlier by Immunex, and I won't go into them further here,  
24 but as you heard, the health assessment questionnaire that  
25 was included in the study included all the questions from

1 two domains of the SF-36, the mental health component and  
2 the vitality component, and these components analyzed  
3 separately did show a tendency to improvement in the  
4 Enbrel-treated group at the highest doses compared to  
5 placebo.

6 I want to talk at this point about several  
7 issues it's important to consider in the efficacy analysis.  
8 The first issue I'd like to bring up are potential  
9 unblinding issues, and I think this was discussed a little  
10 bit before. As you've heard, approximately 40 percent of  
11 subjects receiving Enbrel at therapeutic doses experienced  
12 an injection site reaction, and this is a potential  
13 unblinding effect which could lead to biasing in some of  
14 the assessments, especially the more subjective  
15 assessments. In addition, subjects receiving Enbrel were  
16 found to have early clinical responses, some as early as 2  
17 weeks, and it's possible that this could lead to difficulty  
18 with assessments performed at 3 months.

19 In addition, there were a larger number of  
20 early discontinuations, especially due to lack of efficacy  
21 based on protocol prespecified criteria, a higher number in  
22 the placebo group compared to the active treatment group,  
23 and there were some imbalances seen both in the baseline  
24 use of non-steroidals as well as corticosteroids.

25 I'll address these issues in the slides that

1 are coming up, but before I go on, I'd like just to point  
2 out a few things. One analysis that helps address the  
3 concern about unblinding is the comparison between 10  
4 milligrams and 25 milligrams of Enbrel. The proportion of  
5 patients with injection site reactions is not different in  
6 a major way between these two dose levels, so that there  
7 may be a somewhat less bias in the comparison between these  
8 arms, and the proportion of patients who met the primary  
9 endpoint was statistically significantly different between  
10 these two dose arms.

11 In addition, I want to just point out in terms  
12 of early discontinuation that the FDA analyzed in detail  
13 the criteria of patients who dropped out for protocol  
14 prespecified lack of efficacy and verified that all these  
15 patients did indeed meet the protocol prespecified  
16 criteria.

17 Objective laboratory values can be helpful in  
18 corroborating efficacy assessments. What I'm showing here  
19 are the data on normalization of laboratory values. I  
20 won't go through it in detail, but you can see that higher  
21 proportions of subjects had normalization of their  
22 laboratory values based on the C-reactive protein,  
23 erythrocyte sedimentation rate, hemoglobin, platelet count,  
24 white blood cell count, and albumin. A higher proportion  
25 achieved the normalization in the high-dose Enbrel group

1 compared to placebo. On the other hand, I just do want to  
2 point out as a caveat that, as you know, the placebo  
3 patients were followed for a shorter time because some  
4 dropped out earlier, so the data used to generate a table  
5 like this is based on last observation carried forward, and  
6 that just must be taken into account.

7 In the Phase II study, which was used to  
8 establish the dosing for the Phase III trial, weight  
9 adjustment was made. Weight adjustment was not made in the  
10 Phase III trial, leading to the possibility that heavier  
11 subjects who have a lower weight-adjusted dose may perhaps  
12 have a lower likelihood of responding. This analysis  
13 addresses that concern, and what it does is to subdivide  
14 patients based on weight categories, the E being patients  
15 less than 60 kilograms, H, on the right of each set, being  
16 patients over 85 kilograms. What you can see is that 63  
17 percent of subjects in the higher weight group experienced  
18 ACR 20 responses at 3 months, and there was no clear  
19 neutralization of the tendency to respond in the heavier  
20 patients.

21 As I pointed out, there were two imbalances in  
22 concomitant medications. What I'm showing here are the  
23 response rates at 3 months based on the ACR 20 response in  
24 the subjects who were on corticosteroids at baseline and  
25 throughout the study and those who were not on

1 corticosteroids, and you can see for both groups there was  
2 an increased proportion of subjects in the Enbrel-treated  
3 arms who achieved an ACR 20 compared to placebo.

4           Similar data is shown here for non-steroidal  
5 use, and you can see for patients who did or did not take  
6 non-steroidals during the study, there was a higher  
7 proportion of patients who achieved an ACR 20 response at 3  
8 months in the Enbrel-treated groups compared to placebo.

9           The FDA performed a logistical regression  
10 analysis in order to identify baseline variables which were  
11 and were not predictive of achieving an ACR response at 3  
12 months. The variables in this analysis which were not  
13 predictive of a response include age, body surface area,  
14 weight, height, baseline rheumatoid factor status, and the  
15 study site. Two variables at baseline were predictive of a  
16 response. We found that a high baseline HAQ is associated  
17 with a lower likelihood of an ACR 20 response, and I just  
18 want to remind you that a high baseline HAQ would be  
19 patients with more functional impairment. In addition,  
20 treatment assignment was highly predictive of a response,  
21 where patients assigned to receive the Enbrel treatment  
22 were more likely to achieve a response than placebo.

23           I want to point out that even though high  
24 baseline HAQ was associated with a lower likelihood of ACR  
25 20 response, even patients who had high baseline HAQs were

1 more likely to achieve a response than patients -- of that  
2 group, those who received Enbrel were more likely to have a  
3 response than the placebo patients, but their likelihood  
4 was somewhat lower than patients with lower baseline HAQs.

5 We subsetting responses based on duration of  
6 disease, and this slide shows that both for patients with  
7 shorter duration of disease, 0 to 5, as well as for  
8 patients with disease of longer duration, including  
9 patients with disease duration greater than 10 years, in  
10 all groups there was a higher proportion of responders in  
11 the Enbrel-treated groups compared to placebo.

12 We talked earlier in the presentation about the  
13 responses based on rheumatoid factor status. I'd just like  
14 to show you the data again here. What you can see is, in  
15 the rheumatoid factor-positive patients there was an  
16 increased proportion of patients who responded at 3 months  
17 with an ACR 20 in Enbrel-treated groups compared to  
18 placebo. In contrast, in the rheumatoid factor-negative  
19 patients, approximately 37 percent responded in the high-  
20 dose Enbrel group compared to just over 40 percent in the  
21 placebo group.

22 I want to point out a couple of caveats here.  
23 One is that we're talking about very small numbers of  
24 patients. This was a minority of patients who were in this  
25 category. In addition, in the FDA analysis, it was found

1 that there were some subjects in the rheumatoid factor-  
2 negative population who achieved ACR 50 and ACR 70  
3 responses at 3 months, and that these numbers were somewhat  
4 higher than in the placebo group. On the other hand, it's  
5 very small numbers, and we are very interested in the  
6 committee's thoughts on this information as well as other  
7 information you've heard today.

8 To deal with potential biases, the FDA  
9 conducted three sensitivity analyses based on different  
10 scenarios to test the robustness of the efficacy data. In  
11 the first assessment, placebo subjects who had lack of --  
12 who discontinued due to lack of efficacy but did not meet  
13 protocol prespecified criteria for lack of efficacy were  
14 recategorized as successes. In the second scenario,  
15 subjects included in the first scenario plus subjects with  
16 other non-adverse-event-related discontinuations were  
17 recategorized as successes. In the third analysis, all  
18 subjects meeting protocol prespecified criteria for lack of  
19 efficacy were recategorized as failures, regardless of  
20 whether they did or did not choose to drop out of the study  
21 for lack of efficacy. In all of these scenarios, when the  
22 data were reanalyzed, the efficacy result remained  
23 significant based on these criteria.

24 This slide shows the time course of ACR 20  
25 responses. You've seen this data already. Suffice it to

1 say that ACR 20 responses were seen very early in the  
2 study, and differences were seen between the different  
3 groups throughout the study.

4 This shows the same data in tabular form.

5 In the rheumatoid arthritis guidance document,  
6 a recommendation is made that in addition to assessing  
7 improvement with the study agent at a particular point in  
8 time, that the analysis try to capture responses over time.  
9 In this analysis, the FDA has attempted to capture lasting  
10 ACR 20 responses. These are defined as responses which  
11 last continuously for a period of time. In the graph shown  
12 on the left, it's responses lasting from 2 weeks to 6  
13 months continuously. In the set on the right, it's  
14 responses lasting from 3 months to 6 months continuously,  
15 meaning that there's no assessment in between those times  
16 which falls below at least an ACR 20 response. You can see  
17 that at each time point, there were increases in the  
18 proportion of patients who met these criteria for lasting  
19 responses beginning at Month 6, and even beginning at 2  
20 weeks, lasting through the last assessment at 6 months.

21 I'd like to go on now to briefly discuss the  
22 other two trials that were submitted as evidence of  
23 efficacy, the other two randomized trials. I won't go into  
24 great detail here, because you've heard much of this  
25 information already. I would like to point out that in the

1 Phase II trials, the patient population is the population  
2 with severe, active rheumatoid arthritis, with at least 10  
3 swollen and at least 12 tender joints. All patients who  
4 had failed at least one to four DMARDs, there was a washout  
5 period, and you've heard about the dose categories  
6 previously.

7 As you can see from this graph and as you saw  
8 earlier, a higher proportion of subjects in the high-dose  
9 group achieved an ACR 20 response at 3 months compared to  
10 placebo, and there was a dose-dependent response seen.

11 The next trial I'd like to talk about is the  
12 methotrexate combination trial. You heard about this  
13 earlier. It's a double-blind, randomized trial enrolling  
14 subjects on stable doses of methotrexate, doses of 15 to 25  
15 milligrams weekly, who had active rheumatoid arthritis  
16 despite at least 6 months on methotrexate. Subjects were  
17 randomized to continue methotrexate at the constant doses  
18 and randomized to receive either Enbrel, 25 milligrams  
19 twice a week, or placebo by similar injection. This study  
20 was originally designed to assess safety of combination  
21 therapy; however, during the trial, before the trial was  
22 unblinded, efficacy endpoints were added. The patient  
23 population, based on demographics, was similar to what you  
24 saw before in the Phase III trials. Subjects were around  
25 50 years of age, with disease duration of about 13 years,

1 and the number of failed DMARDs was similar.

2           This is the efficacy data from the methotrexate  
3 combination trial. You've seen this data before. I'll  
4 just point out that ACR 20 responses and ACR 50 responses  
5 both at 3 months and at 6 months were increased in the  
6 Enbrel/methotrexate combination compared to the patients  
7 who had placebo added to methotrexate.

8           So in summary of the efficacy data that I've  
9 presented, the study populations that were assessed in the  
10 three studies submitted to establish evidence of efficacy,  
11 the study populations were similar in these three trials.  
12 They consisted of patients with rheumatoid arthritis of  
13 long duration, patients with severe disease, and patients  
14 who had rheumatoid arthritis that already failed at least  
15 one disease-modifying agent. The studies indicated that  
16 there were increased ACR 20 percent responses at Month 3  
17 and Month 6, increased ACR 50 responses at those same time  
18 points, and increased ACR 20 and ACR 50 percent responses  
19 were seen when Enbrel was combined with methotrexate in a  
20 small Phase II/Phase III trial.

21           I'd like to go on now to discuss the safety of  
22 Enbrel, and this slide lists what I'll be talking about.  
23 I'll begin by discussing the adequacy of population  
24 exposure in the data that was submitted; then go on to  
25 discuss deaths, serious adverse events, and adverse events

1 leading to discontinuation of study agent; then discuss  
2 infections, injection site reactions, malignancies,  
3 autoantibodies and autoimmunity, other adverse events, and  
4 finally talk briefly about anti-Enbrel antibodies.

5           Before I talk about the data, I just want to  
6 mention the guidelines from the International Conference on  
7 Harmonization. This is published in a publication  
8 entitled, "Guideline on Extent of Population Exposure  
9 Required to Assess Clinical Safety for Drugs Intended for  
10 Long-Term Treatment of Non-Life-Threatening Conditions."  
11 This publication recommends minimum long-term exposure at  
12 doses intended for clinical use of 100 subjects studied for  
13 at least 1 year and 300 to 600 subjects studied for at  
14 least 6 months. In addition, a recommendation is made for  
15 total exposure, including short-term exposure and exposure  
16 in other indications, of 1,500 patients.

17           This slide shows the number of patients who are  
18 exposed in the data submitted from Immunex on Enbrel. It's  
19 a total of 1,381 subjects who were exposed. In rheumatoid  
20 arthritis, there were 1,039 subjects exposed, 541 subjects  
21 were treated for 6 months, and 194 subjects were treated  
22 for at least 12 months. The question mark here, I think,  
23 is just due to a change in the software I used where the  
24 greater-than-or-equal sign was changed to 12 months, and I  
25 apologize for that.

1 I also want to point out here that during  
2 product development, after recommendations from the  
3 Arthritis Advisory Committee, the FDA discussed with  
4 Immunex what would be an acceptable safety database to meet  
5 International Conference of Harmonization guidelines, and  
6 based on those discussions, Immunex enrolled additional  
7 patients to their trials to meet the guidelines.

8 Other indications that have been studied with  
9 Enbrel include sepsis, Crohn's disease, HIV infection, and  
10 congestive heart failure.

11 This slide shows the different studies that are  
12 included in the database of safety of Enbrel use in  
13 rheumatoid arthritis. It includes the controlled studies,  
14 213 subjects. These studies I've talked about already. In  
15 addition, it includes the subjects in an ongoing blinded  
16 study of early rheumatoid arthritis patients randomized to  
17 receive either Enbrel or methotrexate. This study is still  
18 blinded. In addition, it includes maintenance phases of  
19 the controlled studies, open-label trials, a dose  
20 escalation trial, a pharmacokinetics study, and a study of  
21 pediatric JRA that you heard about before. These data on  
22 safety in children, I'll be discussing at the end of the  
23 presentation.

24 I need to point out at this point that 12  
25 slides were left out of the copies of the slides that the

1 advisory committee received. It's the next 12. We passed  
2 those out at the break. Some of them are slightly out of  
3 order, but I just want to point it out to avoid any  
4 confusion.

5           First I'll talk about the deaths that were seen  
6 in Enbrel trials, and I'll divide my discussion in  
7 controlled trials and open-label and extension trials. In  
8 the controlled trials, two deaths were seen, both of  
9 myocardial infarction. One patient was receiving placebo,  
10 and one patient was receiving Enbrel. In the open-label  
11 and extension trials, one Enbrel-treated subject died of  
12 ovarian carcinoma, one Enbrel-treated subject died of  
13 staphylococcal sepsis, and I'll talk more about the death  
14 of staphylococcal sepsis later on when I talk about  
15 infections.

16           In the Phase III trial, this slide shows the  
17 serious adverse events that were seen. Two events were  
18 seen in the placebo arm, five events in three subjects were  
19 seen in the 10-milligram Enbrel group, and one serious  
20 adverse event was seen in the high-dose Enbrel group. In  
21 the placebo group, there was one case of dehydration, one  
22 case of bronchitis -- coded as bronchitis. The case was  
23 actually a case of bacterial tracheitis. In the low-dose  
24 Enbrel group, one subject experienced both cholecystitis  
25 and dehydration. One subject experienced GI hemorrhage,

1 and one subject experienced myalgia and right heart failure  
2 as a serious adverse event. The serious adverse event in  
3 the high-dose Enbrel group was cholelithiasis.

4 The adverse events leading to discontinuation  
5 in the Phase III trial are shown here. In the placebo  
6 group, there were three events: a case of lung nodule, a  
7 patient with headache, and a patient with bacterial  
8 tracheitis. In the low-dose Enbrel group, there were five  
9 events leading to discontinuation: one case of rash; one  
10 case of leukopenia -- this was a patient with preexisting  
11 Felty's syndrome; one case of hemoptysis; one headache; and  
12 one case of injection site reaction leading to  
13 discontinuation. In the Enbrel high-dose group, there were  
14 two events leading to discontinuation, one case of pruritus  
15 and one case of hypotension.

16 This slide shows the adverse events that were  
17 seen in the Phase III trial, all adverse events that were  
18 seen at a rate of 5 percent or greater. Two adverse events  
19 appeared to have a higher proportion of patients  
20 experiencing this in the Enbrel-treated patients compared  
21 to placebo. These are infections shown in highlight here,  
22 58 percent of the high-dose Enbrel group, 57 percent of the  
23 low-dose, and 38 percent of placebo. So there did not  
24 appear to be any dose-dependent increase in infections. In  
25 addition, there was a higher proportion of patients who

1 experienced injection site reactions, 49 and 43 percent in  
2 the two Enbrel groups compared to 13 percent of placebo.

3 I need to point out here, as you've already  
4 heard, that the subjects in the placebo group were followed  
5 in many cases for a significantly shorter period of time  
6 compared to the Enbrel-treated group, because many of the  
7 placebo patients dropped out for a number of reasons,  
8 including lack of efficacy. So it's important to keep that  
9 in mind when you consider the higher proportions seen. We  
10 did not adjust this for the duration of exposure compared  
11 to the data that you saw earlier today.

12 This slide shows the different infections that  
13 were seen in patients in the various arms in the Phase III  
14 trial. You already saw that patients with any infection  
15 were increased in the Enbrel-treated groups. In addition,  
16 the proportion of patients having an upper respiratory  
17 infection was increased in the two Enbrel groups, 33  
18 percent and 29 percent versus 16 percent. Looking down the  
19 list, you can also see that there were more cases of  
20 vaginitis and cystitis in the Enbrel-treated groups  
21 compared to placebo, 5 percent each in the high-dose Enbrel  
22 group, 0 percent in the placebo group. Keep in mind,  
23 however, that the Enbrel-treated patients were followed for  
24 a longer period of time.

25 I want to point out a couple of other things.

1 When FDA reviewed the severity and use of antibiotics of  
2 the patients experiencing an upper respiratory infection in  
3 the different groups, there did not appear to be any  
4 difference in severity between these groups or any  
5 difference in the use of antibiotics.

6 This slide shows the frequency of infection, on  
7 top, and the grade of infection, on the bottom, of patients  
8 in the different arms of the trial. You can see that most  
9 of the subjects with infections had one or two episodes,  
10 but 8 percent of subjects in the Enbrel 25-milligram arm  
11 had three infections, and one had four or greater. This  
12 was a single subject who had vaginitis for several times in  
13 the trial.

14 The bottom part of the slide shows the grade of  
15 infections. All the infections were Grade 1 and 2 in the  
16 controlled 6-month portion of this trial. There were no  
17 Grade 3 and 4 infections. I'd like to point out that a  
18 Grade 3 infection, generally speaking, was a subject with  
19 infection requiring hospitalization or IV antibiotics, and  
20 a Grade 4 infection was a life-threatening infection.

21 A concern has been raised, based on the  
22 mechanism of action of this agent -- namely, blocking TNF  
23 -- of the possibility that to the extent that tumor  
24 necrosis factor plays an important role in host defenses,  
25 that it's important to assess the degree to which Enbrel

1 and other agents that block TNF might increase the number  
2 of serious infections as well as the severity of  
3 infections. Most of the data that I'll be talking about in  
4 the next few slides is based on the uncontrolled extension  
5 trials and the uncontrolled open-label trials. So there's  
6 no control group, and it's important to keep that in mind.

7           The FDA went and tabulated all the serious  
8 infections. This is generally based on infections  
9 requiring hospitalization or requiring intravenous  
10 antibiotics that were not for prophylactic use. Nineteen  
11 serious infections were identified in 17 subjects. There  
12 were three cases each of pyelonephritis or urinary tract  
13 infection, cellulitis, wound infection, and pneumonia. Two  
14 cases each were seen in this group of septic arthritis, and  
15 there was one case each of bronchitis, abdominal abscess,  
16 osteomyelitis, and foot abscess. There was one case of  
17 staphylococcal sepsis that you heard about briefly earlier,  
18 which resulted in a death.

19           I want to point out, as I did earlier, that  
20 it's difficult to evaluate the drug-relatedness of these  
21 serious infections, because there's no control group. I'd  
22 also like to point out that in the FDA review, several  
23 infections were noted which were of particular concern,  
24 including the death, as well as two cases which appear to  
25 have an unusually prolonged course and were refractory to

1 treatment, and I'll talk about those three cases in the  
2 next few slides.

3           The first case was a 54-year-old woman who died  
4 of staphylococcal sepsis. She had been on Enbrel for a  
5 total of 353 days of exposure, and at the time of the  
6 event, she was on prednisone 10 milligrams a day and  
7 receiving a non-steroidal. Previously, she had had a left  
8 shoulder arthroscopy and developed a staph wound infection  
9 as a complication of that procedure. She developed left  
10 knee pain later on, after the staph wound infection  
11 resolved. When she developed the left knee pain, she  
12 visited her primary care physician, who diagnosed this as a  
13 rheumatoid arthritis flare. He increased her prednisone  
14 dose from 10 milligrams a day to 20 milligrams twice a day,  
15 or 40 milligrams a day. She was subsequently hospitalized  
16 with hypoxia and septic arthritis of all her prosthetic  
17 joints, and in the hospital she deteriorated and died,  
18 despite receiving intravenous vancomycin and nafcillin, to  
19 which the staphylococcus was sensitive. No source of  
20 infection was identified; however, an infectious disease  
21 consultant noted several possible portals of entry,  
22 including sites of excoriation on the lower extremities at  
23 the site of an injection site reaction.

24           The next patient is a patient with cellulitis  
25 and osteomyelitis. This patient was a 75-year-old woman

1 with longstanding rheumatoid arthritis, first diagnosed in  
2 1950. Her previous treatments include oral  
3 corticosteroids, azathioprine, and methotrexate. At the  
4 time of the event, she had been on Enbrel for 444 days.  
5 She developed cellulitis at the site of trauma, and despite  
6 prolonged antibiotic therapy, she developed an ulcer at the  
7 infection site and osteomyelitis. The infection did  
8 resolve, and the ulcer healed ultimately, after 6 months of  
9 receiving antibiotics.

10           The third and final case I'd like to present is  
11 a 48-year-old man with rheumatoid arthritis for 9 years,  
12 who previously received oral corticosteroids and numerous  
13 DMARDs. His concomitant medications at the time of the  
14 event were non-steroidals and low-dose prednisone. He had  
15 been receiving Enbrel for a total of 274 days. This  
16 patient developed an abscessed tooth, which was treated  
17 with penicillin V for 8 days. In spite of that, 3 weeks  
18 later the patient developed staphylococcal cellulitis at  
19 his left cheek, which was treated with multiple courses of  
20 antibiotics because of failure to resolve. Ultimately, the  
21 infection did resolve after 3 months.

22           To try to give more information to assess these  
23 serious infections, we present here an analysis of the  
24 incidence of serious infections over time. This is the  
25 same data, presented slightly differently, that you saw

1 earlier from Immunex. Here the cases of serious infection  
2 were divided based on 3-month periods of exposure, up to 3  
3 months, 3 to 6 months, 6 to 9 months, and so on. The  
4 number of patients exposed for that period of time are  
5 shown here, and the cases are shown in the third line.

6 What you can see in the last line, where an  
7 incidence is calculated, the incidence varied from 0.8  
8 percent up to 1.6 percent, 1.8 percent at the last time  
9 point, but there does not appear to be any clear trend to  
10 increasing nor to decreasing infection -- sorry, no trend  
11 to increasing or decreasing incidence with longer durations  
12 of Enbrel exposure.

13 I'd like to point out in addition that it's  
14 possible that since this is uncontrolled data, that you're  
15 getting a selection of patients over time, so the data must  
16 be taken with a grain of salt, and also it is rather small  
17 numbers, especially at the later time point. But I still  
18 want to present it, because it's at least some data to  
19 address this question.

20 Before leaving the concern about infections  
21 with Enbrel, I just want to point out data from an earlier  
22 trial in sepsis when Enbrel was being considered for use in  
23 sepsis. I won't go through this trial in great detail, but  
24 I just want to point out that this is a very different  
25 patient population than we're considering today for

1 rheumatoid arthritis. This trial I'm talking about in  
2 sepsis was a critically ill patient population. In this  
3 trial, a dose-dependent increase in mortality was observed.  
4 The deaths that occurred in this trial appear to be due to  
5 the sepsis syndrome.

6 I mention this at this point because of the  
7 possibility that since TNF plays a role in host defenses,  
8 that blocking TNF could theoretically have an effect on the  
9 number of infections and the severity of infections that  
10 are seen, and I just present it for your consideration.

11 In conclusion, the data I've presented showed  
12 an increased incidence of infection in the Enbrel-treated  
13 patients in the 6-month Phase III trial. This was  
14 predominantly due to an increase of upper respiratory  
15 infections, which was seen both in the Phase II trial and  
16 in the Phase III trial. One death of staphylococcal sepsis  
17 was seen, and 19 serious infections were seen in the  
18 exposed patients overall. I think it's difficult to reach  
19 definite conclusions about the drug-relatedness of these  
20 infections because of the lack of a control group for most  
21 of the serious infections that were seen.

22 I'll move on now to other infections. As I  
23 mentioned earlier, there was a higher proportion of  
24 patients with injection site reactions. You heard about  
25 this extensively earlier today. Approximately 30 percent

1 of patients who had an injection -- sorry, 30 percent had  
2 one to five injection site reactions, approximately 5  
3 percent had six to ten, but still somewhere around 10  
4 percent or so had more than 10 injection site reactions.  
5 The severity of the injection site reactions is shown at  
6 the bottom. They were all Grade 1 and Grade 2, Grade 1  
7 being defined as erythema only, Grade 2 being defined as  
8 erythema plus either pain, phlebitis, or swelling.

9 Injection site reactions were seen in  
10 approximately 40 percent of subjects across studies. As I  
11 said, they were all Grade 1 and Grade 2. In addition,  
12 rashes were seen in 7 to 20 percent of subjects, and this  
13 led to five discontinuations in the clinical trial  
14 experience overall. Twenty-four events were observed which  
15 were of possible allergic nature. These included cases of  
16 facial swelling, puffy eyes, and hives. Of these 24  
17 events, two led to withdrawal, and in 22 of the cases  
18 treatment was continued. In those 22 continuations, no  
19 recurrences were seen. And the incidence of severity of  
20 the injection site reactions did not appear to be dose  
21 dependent when the 10-milligram and 25-milligram arms were  
22 compared.

23 A concern has been raised with some  
24 immunosuppressive agents used in treating rheumatoid  
25 arthritis that there may be an increased incidence of

1 malignancies. For this reason, I'd like to present the  
2 data on malignancies seen in the clinical trial experience  
3 with Enbrel. Thirteen malignancies were observed overall.  
4 One of these was in the placebo arm of the methotrexate  
5 combination trial. Of the 12 remaining cases on Enbrel,  
6 five were basal cell carcinoma in subjects who had  
7 preexisting basal cell carcinoma. Of the seven remaining  
8 cases of carcinoma, as you heard earlier, two were ovarian  
9 carcinoma, and the others were one each of breast, lung  
10 carcinoma, prostate carcinoma, Hodgkin's disease, and bile  
11 duct carcinoma.

12 The incidence over time is shown in this slide  
13 in 6-month intervals, and you can see that there does not  
14 appear to be any clear trend toward increasing incidence  
15 with longer duration of exposure to Enbrel.

16 Concern has been raised with agents that block  
17 TNF, as you heard earlier, about increases in  
18 autoantibodies, and two cases have been seen with other  
19 agents that block TNF of new autoimmune disease. There's  
20 one case of pericarditis and one new case of polyarthritiis.  
21 I'll be going through in the next few slides the data that  
22 the FDA reviewed on autoantibody production and new  
23 autoimmune disease in the Enbrel experience.

24 The autoantibodies that were measured are shown  
25 here, as you've already seen -- antinuclear antibodies,

1 anti-double-stranded DNA antibodies, both by  
2 radioimmunoassay and by the crithidia assay, which is more  
3 sensitive, and anticardiolipin assays were measured -- and  
4 I just want to mention at this point that looking at the  
5 clinical data, no new autoimmune diseases were observed,  
6 and no new autoimmune disease symptoms were seen in the  
7 Enbrel-treated patients.

8           This slide shows the data for antinuclear  
9 antibodies. You can see that there was a higher proportion  
10 of subjects with a new positive ANA in the 25-milligram  
11 dose arm of Enbrel compared to placebo, 12 percent compared  
12 to 5 percent. In the low-dose arm, the proportion was  
13 similar.

14           Looking at anti-double-stranded DNA by  
15 radioimmunoassay, you can see that there was a higher  
16 proportion of subjects with new positive anti-double-  
17 stranded DNA in both the 10-milligram and 25-milligram  
18 Enbrel doses, 12 percent in each of these arms compared to  
19 4 percent in placebo.

20           In the next three slides, I'd like to show you  
21 the actual titers over time of anti-double-stranded DNA.  
22 The first slide shows the six subjects in the placebo arm  
23 who had at least one measurement of anti-double-stranded  
24 DNA that was increased over baseline. The Y axis is the  
25 anti-double-stranded DNA titers, the X axis shows time in

1 days, and the line at the bottom, ULN, is the upper limit  
2 of normal. You can see that the placebo patients who had  
3 positive anti-double-stranded DNA were generally very low  
4 in titer, with the exception of Patient 1202, who had  
5 higher but constant levels.

6           These are the data on the 15 subjects in the  
7 10-milligram Enbrel arm who had any measurement of anti-  
8 double-stranded DNA which was elevated over the upper limit  
9 of normal. You can see that there were some patients with  
10 high titers, but I also want to point out that the titers  
11 were highly variable, and some of the titers went up at 3  
12 months and came back down again at later time points. We  
13 did not see a clear trend toward increasing titers of anti-  
14 double-stranded DNA in this arm, as well as in the 25-  
15 milligram dose arm, which is shown here. Again, there were  
16 some patients with increased titers, you can see, at the 3-  
17 month time point. Some of these patients came down again  
18 in later measurements.

19           In conclusion for autoantibodies -- I'm sorry,  
20 this is some more data. The sera that were collected  
21 during the trial were retested later on for reactivity in  
22 the more specific crithidia luciliae assay for anti-double-  
23 stranded DNA. This assay is more specific both for anti-  
24 double-stranded DNA antibodies and for lupus. In this  
25 assay, none of the 27 placebo patients tested were

1 positive, four of the 31 Enbrel 10-milligram patients were  
2 positive, and three of the 33 Enbrel 25-milligram subjects  
3 were positive. All of these subjects were negative at  
4 baseline, except for one of the 10-milligram subjects, the  
5 one who had preexisting lupus that you heard about earlier.

6 So, in conclusion, looking at several  
7 autoantibodies, a higher number of Enbrel subjects  
8 developed positive antinuclear antibodies and elevated  
9 anti-double-stranded DNA antibodies compared to controls.  
10 Similar results were seen with anticardiolipin antibody,  
11 both of the IgM and the IgG class. Few subjects were seen  
12 who had a rising titer of autoantibodies on serial  
13 measurements. No Enbrel-treated subject with  
14 autoantibodies developed new clinical autoimmune disease or  
15 new autoimmune disease symptoms. Long-term follow-up may  
16 help elucidate the clinical significance of these  
17 autoantibodies.

18 Turning now to anti-Enbrel antibodies, I just  
19 want to point out as background that many proteinaceous  
20 agents as well as other therapeutic agents cause induction  
21 of antibodies to the therapeutic agent. In some cases,  
22 this can neutralize the clinical effect. In this study,  
23 409 subjects were tested for anti-Enbrel antibodies, and  
24 five of those subjects were found to be positive. As you  
25 heard earlier, none of these five subjects with anti-Enbrel

1 antibodies had neutralizing antibodies. Some of the  
2 antibody-positive subjects were responders based on the ACR  
3 20 response. No subjects were observed who had a response  
4 which was reversed after antibodies were detected. The FDA  
5 has some concerns about the sensitivity of this assay, and  
6 the sponsor is currently working on improving the  
7 sensitivity of the assay.

8           So in summary of the safety portion of my talk,  
9 regarding the controlled studies, an increased incidence of  
10 infection was seen overall and of upper respiratory tract  
11 infections in particular. An increased proportion of  
12 patients with injection site reactions was seen, and a  
13 higher proportion of subjects with autoantibodies was seen.  
14 However, no increase was seen in severe infections in  
15 controlled studies, and there was no increase in severe  
16 adverse events or in deaths. In addition, in the  
17 controlled studies, no new autoimmune disease symptoms were  
18 seen, and no evidence was seen of anti-Enbrel antibodies  
19 which reverse the clinical effects of the product.

20           In open-label studies, one death was seen of  
21 staphylococcal sepsis. Nineteen severe infections were  
22 seen overall. Several cases were seen with an apparently  
23 prolonged course, which appeared to be poorly responsive to  
24 treatment. And as I mentioned, the drug-relatedness of  
25 these cases is difficult to assess because of the lack of a

1 control group. In addition, seven non-basal cell  
2 malignancies were seen, and no control data is available on  
3 the relative risk compared to untreated controls.

4 In the last few slides, I'd like to go on to  
5 discuss the trial that was carried out with children with  
6 juvenile rheumatoid arthritis, and before I talk about the  
7 trial and the data, I'd like to point out that there's an  
8 effort in process to gain more information on products that  
9 are licensed for adults when those products are likely to  
10 be used in children. I think Immunex needs to be commended  
11 for carrying out a study of safety and dosing in children  
12 and to have submitted the data at the time of submission  
13 for licensure of their product, which is fairly unusual.

14 The trial that was submitted was a two-phase  
15 trial. The first part is an open-label study, and the  
16 second part is a randomized withdrawal study for subjects  
17 who have a response in the initial open-label trial. The  
18 data that were submitted to the agency, which I will be  
19 discussing, are exclusively from the first part of this  
20 trial, the 3-month open-label study.

21 This study was a multicenter study of Enbrel  
22 given twice weekly for 90 days at a dose of 0.4 milligrams  
23 per kilogram. This dose is equivalent to the 25-milligram  
24 dose in adults. The inclusion criteria were for  
25 polyarticular-course juvenile rheumatoid arthritis patients

1 based on ACR definition. The subjects were aged 4 to 17.  
2 All subjects were refractory to methotrexate or intolerant  
3 of methotrexate. Again, I apologize for the question mark.  
4 It's just due to the software change. All subjects had at  
5 least five swollen joints and at least three joints with  
6 limitation of motion and in Steinbrocker functional Class I  
7 to III.

8           The open-label portion of this trial that I'll  
9 be discussing measured population pharmacokinetics,  
10 measured a 90-day response using the juvenile rheumatoid  
11 arthritis definition of improvement -- namely, a greater  
12 than or equal to 30 percent response in three of the six  
13 following: physician and patient global assessment; active  
14 joint count; limitation of motion in joints; functional  
15 assessment based on the childhood health assessment  
16 questionnaire; erythrocyte sedimentation rate; with a  
17 greater than or equal to 30 percent worsening in no more  
18 than one of these parameters. The safety data that was  
19 collected was based on the pediatric National Cancer  
20 Institute toxicity scale and assesses infections, injection  
21 site reactions, allergic reactions, constitutional  
22 symptoms, and autoantibodies.

23           These are the responses that were seen in the  
24 open-label trial. You can see that overall for this  
25 population of patients with polyarticular-course JRA, a 76

1 percent improvement was seen at the 3-month time point, and  
2 percentages ranging from 50 to about 80 percent were seen  
3 in the three different onset subsets.

4 This slide presents the serious adverse events  
5 that were seen in the JRA trial. Two patients were seen  
6 who developed aseptic meningitis following varicella  
7 infection. Both of these patients resolved without -- both  
8 of these cases resolved without sequelae. One patient  
9 developed vertebral artery thrombosis. This was documented  
10 to be related to cervical subluxation, and their  
11 anticardiolipin antibody was negative at the 90-day time  
12 point. One patient was hospitalized for gastroenteritis,  
13 and one patient developed a Grade 3 thoracic compression  
14 fracture, and this patient had been on long-term  
15 corticosteroids.

16 The adverse events were compared to adult  
17 adverse event data of the constitutional symptoms.  
18 Abdominal pain and vomiting were more frequent in juvenile  
19 rheumatoid arthritis patients than in adults, abdominal  
20 pain seen in 17 percent compared to 7 percent of adults,  
21 vomiting seen in 14.5 percent of children versus 3 percent  
22 of adults. No difference in frequency or severity of  
23 infections was seen. No difference was seen in injection  
24 site reactions or development of autoantibodies between  
25 juvenile rheumatoid arthritis and adult RA. No association

1 of adverse events in JRA patients was seen both with regard  
2 to age or with regard to disease onset subsets.

3 In summary for the pediatric data, the  
4 polyarticular-course JRA patients studied demonstrated  
5 responses to Enbrel in a 90-day open-label study that were  
6 comparable to adult rheumatoid arthritis patients who were  
7 studied in randomized, controlled trials. Enbrel appears  
8 to have a safety profile in JRA patients which is  
9 comparable to adult rheumatoid arthritis, except more  
10 gastrointestinal intolerance was observed. Long-term  
11 safety in JRA patients is not currently available.

12 I'd like to stop there. The next presentation  
13 will be by Dr. David Green regarding the pharmacokinetics.

14 DR. GREEN: I'm David Green. I'm going to talk  
15 about selected aspects of Enbrel's pharmacokinetics  
16 briefly.

17 The pharmacokinetics of Enbrel are proposed at  
18 a dose of 25 milligrams as the standard dose, to be given  
19 subcutaneously. It's going to be given twice weekly, which  
20 means the dosing interval is 84 hours. According to the  
21 principles of pharmacokinetics, drug accumulation will be a  
22 function of the dosing interval and the half-life, and  
23 since the dosing interval is fixed in this case, the  
24 variable is the half-life, and this will be determined by  
25 the individual patient and, as a consequence of this, will

1 dictate pharmacokinetic effects such as accumulation. The  
2 half-life of Enbrel is thought to be 70 hours based upon a  
3 subcutaneous administration to healthy volunteers.

4 Therefore, it's expected that with repeated administration,  
5 serum levels would accumulate approximately two-fold with  
6 repeated dosing in comparison to those of a single dose.

7 The pharmacokinetics that are available on an  
8 individual-patient basis with repeated dosing is very  
9 limited, and even the limited amount of information has  
10 significant limitations in the amount of information that  
11 we can obtain from the data. These data suggest that  
12 patients with rheumatoid arthritis have a variable half-  
13 life which is often greater than 70 hours. Furthermore, as  
14 a consequence of this, the longer the half-life on an  
15 individual basis, the greater the extent of drug  
16 accumulation with repeated dosing. The consequences of  
17 higher drug levels are presently unknown.

18 I'm going to talk about two studies that were  
19 conducted in rheumatoid arthritis and a third study on  
20 pharmacokinetics in a different disease population. The  
21 first study is a Phase I study in patients with rheumatoid  
22 arthritis. This was a dose escalation study that was  
23 comprised of 15 patients. There were three to six patients  
24 per dose group, there were four dose groups, and they  
25 ranged from 2 to 16 mg/m<sup>2</sup>. The drug was administered

1 subcutaneously, and it was given twice weekly for 4 weeks.

2 This study provides us an opportunity to  
3 directly observe the half-life in this patient population,  
4 as after the final dose, six samples were collected at the  
5 time periods indicated, 24 to 144 hours. It was noted that  
6 peak serum levels occurred at 72 hours or prior to that.  
7 Therefore, the interval between 72 hours and 144 hours was  
8 during the elimination profile for the drug, and,  
9 therefore, it provided us an opportunity to test the  
10 hypothesis that over one half-life -- that is, 72 to 144  
11 hours -- serum concentrations would drop by 50 percent or  
12 greater. Therefore, the hypothesis was as stated, that at  
13 70 hours serum concentrations would be 50 percent or less.  
14 Too few samples were collected to actually estimate the  
15 half-life.

16 In the histogram that is presented here, you  
17 can see the number of patients on the Y axis versus the  
18 percent change over one half-life. Eight of 15 patients  
19 did indeed show a 50 percent decrease over the 70-hour  
20 period. The remainder indicated they had half-lives  
21 greater than 70 hours. Of the three patients who were  
22 given the highest dose, 16 mg/m<sup>2</sup>, approximately the 25-  
23 milligram dose proposed for use, two had serum levels of 70  
24 and 90 percent at the end of the collection period. Of the  
25 one remaining individual given the 16 mg/m<sup>2</sup>, their

1 observation period ended at 120 hours; therefore, they were  
2 only observed for 50 hours, but their level was 87 percent  
3 at that time.

4           The other study that was conducted with a  
5 reasonable amount of sampling in RA patients was a Phase I  
6 study -- let me back up. This study leads to the  
7 conclusion that the half-life in rheumatoid arthritis  
8 patients is heterogeneous and it covers a range, and that  
9 some individuals are likely to experience higher-than-  
10 predicted drug levels.

11           The second study was a pharmacokinetic and  
12 bioavailability study also conducted in rheumatoid  
13 arthritis patients. This study was a single-dose study of  
14 subcutaneously administered Enbrel, in which doses of  
15 either 10 or 25 milligrams were used. It was an I125-  
16 labeled Enbrel, and the sponsor did calculate half-lives  
17 for each of the doses that were incorporated in the study.  
18 The half-life for the 10-milligram dose was 102 hours, and  
19 the half-life for the 25-milligram dose was 171 hours. If  
20 one were to use the half-life reported for the 25-milligram  
21 dose, the extent of accumulation that would be estimated  
22 would be 3.4 over a single dose. Again, the half-life was  
23 not reliably estimated in this study and so may be expected  
24 to be in fact longer.

25           The final study, which looked at repeated

1 subcutaneous administration of Enbrel, was conducted in a  
2 different five-patient population, and this was in HIV-  
3 positive patients, and it was a twice weekly dosing regimen  
4 conducted over 8 weeks. It used a variety of doses which  
5 ranged from 0.125 to 1.25 mg/m<sup>2</sup>. To incorporate all the  
6 information from this study, since a variety of doses were  
7 used, a standardization procedure was incorporated by FDA,  
8 and that is, the observed serum levels were divided by the  
9 dose. Then comparable time periods were compared at Week 7  
10 as to those during Week 1. The average increase of Week 7  
11 to Week 1 was found to be 3.4-fold higher, with a range in  
12 individuals of 1 to 11.6.

13 Remembering that the serum half-life and dosing  
14 interval are the important components in determining the  
15 extent of accumulation following repeated dosing, we have  
16 to be concerned about the variability among individual  
17 patients. The available data suggests that the half-life  
18 among these patients varies significantly. At present, the  
19 magnitude of accumulation and the percentage of patients  
20 not conforming to the pharmacokinetics expected or just  
21 presently thought of are unknown. The effects of  
22 accumulation upon Enbrel's safety and efficacy have not  
23 been established.

24 An important consideration to bear in mind in  
25 the discussions on pharmacokinetics is not whether the

1 pharmacokinetics are predictable, but whether we have  
2 sufficient information to make reasonable predictions.

3 Thank you.

4 DR. PETRI: Let me ask the committee if there  
5 are questions for purposes of clarification for either Dr.  
6 Siegel or Dr. Green, and I'll start with Dr. Silverman,  
7 followed by Dr. Yocum.

8 DR. SILVERMAN: I have two questions, one for  
9 each of the presenters.

10 DR. PETRI: Perhaps I can ask both presenters  
11 to stay by the podium for the questions.

12 DR. SILVERMAN: For Dr. Siegel, in one of the  
13 summaries received for JRA, there were 69 patients.  
14 Thirteen patients, however, had less than -- did not meet  
15 the entry criteria of loss of range of motion, and three  
16 patients did not meet the entry criteria of not having less  
17 than or equal to 10 milligrams of prednisone. How were  
18 these patients dealt with in your analysis?

19 DR. JEFF SIEGEL: I'd like to ask the clinical  
20 reviewer, Lisa Rider, who reviewed the safety data, to  
21 address this question.

22 DR. RIDER: Those patients were included in the  
23 analysis, but when excluding them, the results remained  
24 essentially the same.

25 DR. SILVERMAN: How could they be included when

1 one of the major outcome variables is not met? I mean, if  
2 they don't meet entry criteria, shouldn't our analysis be  
3 on less? Well, philosophical.

4 Next question is to Dr. Green, and that was,  
5 did you do any data on the PK in JRA? Any analysis of that  
6 data?

7 DR. GREEN: Well, the data that's available in  
8 JRA were incorporated into a population pharmacokinetics  
9 model, and there are discussions under way regarding  
10 different approaches to that data, but it's clear that the  
11 JRA population has a decreased clearance.

12 DR. SILVERMAN: And did you break it down at  
13 all by age?

14 DR. GREEN: By age? Yes. Again, that analysis  
15 is being scrutinized by FDA in terms of the variables such  
16 as weight and age to be incorporated into the population  
17 pharmacokinetics model.

18 DR. PETRI: Dr. Yocum is next.

19 DR. YOCUM: I have three questions, the first  
20 of Jeff. My understanding of the sepsis trial with Enbrel  
21 was in fact there were greater numbers of death in the  
22 treated group. Am I wrong on that, or was that --

23 DR. JEFF SIEGEL: If you had a different  
24 impression from my presentation, I apologize. The data are  
25 that there was a dose-dependent increase in mortality in

1 the Enbrel-treated patients.

2 DR. YOCUM: In the sepsis trial.

3 DR. JEFF SIEGEL: In the sepsis trial.

4 DR. YOCUM: Okay.

5 DR. JEFF SIEGEL: If I said something  
6 different, I misspoke.

7 DR. YOCUM: Okay. Second question, again,  
8 Jeff, we really have a paucity of laboratory data -- in  
9 fact, nothing -- as far as liver function, renal function,  
10 and were these double-stranded DNA antibodies associated  
11 with anything which might suggest any renal disease or  
12 other things that one might be worried about?

13 DR. JEFF SIEGEL: The laboratory data was  
14 carefully scrutinized for patients with abnormalities at  
15 the Grade 3 and 4 level. There was no pattern of  
16 laboratory abnormalities seen.

17 DR. YOCUM: Okay.

18 Final question, for Dr. Green, is, in this  
19 assay of Enbrel level -- and this may be total naivete on  
20 my part -- does rheumatoid factor at all react with the Fc  
21 portion of this? And if that's a possibility and we don't  
22 even know what the IgG rheumatoid factor may have to do  
23 with this, is there any -- how do you rule all that out,  
24 and how do you really look at PK with this as an issue, if  
25 it is an issue?

1 DR. GREEN: I think the company could probably  
2 address the specific issues regarding the assay with more  
3 detail than I have. My understanding is that there is some  
4 concern -- greater or smaller, I think the company could  
5 probably respond to that -- about potential interferences  
6 and about potential species that might be formed with  
7 Enbrel. I think the information that's available suggests  
8 that given the amount of rheumatoid factor patients who are  
9 positive versus those who are negative, we basically have  
10 an understanding of one group because of its predominance  
11 in a number of individuals.

12 DR. PETRI: Let me ask, does Dr. Hayes want to  
13 respond further to that question?

14 DR. YOCUM: I'm only interested because of the  
15 separation of the rheumatoid factor-negative/positive  
16 patients and whether there's some sort of interaction in  
17 that.

18 DR. HAYES: No.

19 DR. PETRI: Thank you.

20 Dr. Frieri?

21 DR. FRIERI: I have a few questions on the  
22 events in terms of the increased cough and the URIs, for  
23 Dr. Siegel. Do we know if these patients were atopic? And  
24 since rhinovirus can increase IL-8 production and maybe be  
25 somewhat related by biofeedback with TNF going down and IL-

1 8 going up, do we know if there's an atopic event to  
2 explain the increased incidence of URI, but not necessarily  
3 rhinitis?

4 DR. JEFF SIEGEL: I don't have anymore  
5 information about that in particular. The only other  
6 information I can give you is that the patient with  
7 hemoptysis was a patient with preexisting bronchiectasis  
8 who went on trial and experienced increased cough. She had  
9 that for a period of time and then had an episode of  
10 hemoptysis, and that led to discontinuation of the agent.

11 In terms of the other episodes of cough, I  
12 don't really have any other information.

13 DR. FRIERI: Do we know if it's a BHR,  
14 bronchial hyperresponsiveness, which could also be a sign  
15 of atopy or asthma?

16 DR. JEFF SIEGEL: I think that's a good  
17 question. We don't have anymore information.

18 Does the company have anymore information in  
19 this regard?

20 DR. HAYES: We did have patients in the --

21 DR. PETRI: I'm sorry, Dr. Hayes, if you could  
22 go to one of the microphones, please.

23 DR. HAYES: We had no exclusion from this trial  
24 for atopic or patients with asthma, and we did have  
25 patients who had asthma and allergic rhinitis, et cetera,

1 entered into this trial. It was not an exclusion criteria.  
2 And as many of you know if you deal with COSTART, if a  
3 patient comes in and says, "Oh, I've had a cough this  
4 morning," that gets coded as cough increase, and it could  
5 have been -- we did not look specifically at those.

6 DR. PETRI: Dr. White, followed by Dr. Liang.

7 DR. WHITE: Jeff, I have a particular concern  
8 that the data from the methotrexate/Enbrel combination  
9 trial are not adequate to draw conclusions about safety or  
10 efficacy. In particular, from what you've presented, they  
11 had 57 patients followed for 6 months rather than the 300  
12 to 600. What is the FDA's written or unwritten view on  
13 safety? If that request is for wording, for labeling that  
14 has to do about combination, how do you --

15 DR. JEFF SIEGEL: Okay. Let me give a  
16 provisional answer, and then I'll ask Jay Siegel to give a  
17 definitive policy answer.

18 (Laughter.)

19 DR. JEFF SIEGEL: Since methotrexate is a very  
20 commonly used drug in rheumatoid arthritis, it's our policy  
21 to request that agents being considered for licensure have  
22 some experience in methotrexate, because it's likely that  
23 those agents will be used in combination. The trial that I  
24 presented was not intended to establish safety or efficacy  
25 with methotrexate co-administration. So the trial that was

1 designed was at least to get a minimal degree of  
2 information about safety with combinations, and we're very  
3 interested in the panel's comments about further trials  
4 that you would like to see.

5 Jay, do you want to add anything else?

6 DR. JAY SIEGEL: Just to say that written  
7 guidelines, to the extent that we have them, about  
8 population exposure do not specifically quantitatively  
9 address the issue of specific combinations. The numbers  
10 you saw before you were not designed to specifically  
11 address combinations. When we look at likely combinations,  
12 factors such as the scope of toxicities of the individual  
13 drugs and the potential for interactions all play  
14 importantly in deciding the adequacy of the data.

15 DR. WHITE: I do raise that issue because it  
16 strikes me that that's indeed how many rheumatologists  
17 would like to end up using this drug perhaps, and it is my  
18 first-pass view that 57 is probably not a large number of  
19 patients to include written language that would relate to  
20 safety. I also am concerned that assessing efficacy as a  
21 combo, if that's the labeling, that it's efficacious in  
22 combination with methotrexate, I would guess -- Barbara, I  
23 don't know what you think -- biostatisticians would have  
24 trouble with a single trial with 57 versus 24 completed  
25 patients.

1 DR. PETRI: This may actually come up in one of  
2 the discussion questions, so I think we should discuss it  
3 at that point.

4 Dr. Liang, did you have a question?

5 DR. LIANG: Jeff, I missed, what is your  
6 dependent variable in your logistic model? Is that some  
7 kind of a response?

8 DR. JEFF SIEGEL: Is Vance Berger here?

9 DR. LIANG: Did you use the 20 or --

10 DR. JEFF SIEGEL: Oh, I'm sorry. Actually, no,  
11 and I think that Dr. Vance Berger should address this.

12 DR. BERGER: It was ACR status, which, as Dr.  
13 Siegel presented before, takes on four ordered categories:  
14 70 or more, 50 or more but not 70, 20 or more but not 50,  
15 and below 20. So it was the full spectrum of four  
16 categories.

17 DR. LIANG: And did you look at infections, by  
18 any chance, using sort of multivariable techniques?

19 DR. BERGER: Can you repeat the question,  
20 please?

21 DR. LIANG: Did you look at infections, like  
22 the serious ones, in terms of a predictive model?

23 DR. JEFF SIEGEL: I should point out that most  
24 of the serious ones were not in the controlled trial, so it  
25 would be hard to do -- oh, you mean in the uncontrolled

1 data?

2 DR. LIANG: Well, actually, in all of it.

3 DR. JEFF SIEGEL: I think the answer is that we  
4 did not.

5 Do you have any further comments, Vance?

6 DR. BERGER: No, you're correct.

7 DR. PETRI: Okay. Dr. Pucino, followed by Dr.  
8 Simon.

9 DR. PUCINO: Another question for Jeff. If the  
10 half-life data that was presented with the 25-milligram  
11 dose is about 7 days, what happens -- do we have data going  
12 out farther than 2 months for the 0004 study? In other  
13 words, the concern with a slow taper and ultimately  
14 rebounding?

15 DR. JEFF SIEGEL: Do you mean with --

16 DR. PUCINO: With more of the response.

17 DR. JEFF SIEGEL: Okay. I'm sorry, could you  
18 repeat the question? I didn't quite --

19 DR. PUCINO: I guess the drug is tapering  
20 itself almost over a month, and the first study that was  
21 presented, the 0004 trial, presented data after stopping  
22 the drug only up to 2 months. Is there data subsequent to  
23 that?

24 DR. JEFF SIEGEL: We didn't review that data.  
25 Maybe Immunex could comment on that.

1 DR. HAYES: We have no data beyond 2 months,  
2 but this was looked at, and actually the return of symptoms  
3 is compatible with a half-life of 3 and a half to 4 days.

4 DR. PUCINO: And do you know anything about --  
5 realizing that tumor necrosis factor levels are usually not  
6 detectable, during treatment do we see any levels either in  
7 the joints or in the circulation?

8 DR. HAYES: We have not measured in this  
9 patient population TNF levels in joints, and as you know,  
10 patients with rheumatoid arthritis do not usually have  
11 detectable circulating levels of TNF. We did look in Study  
12 0002 at the patients that were in the original Phase I  
13 study. None of those patients at baseline had circulating  
14 levels of TNF.

15 DR. PETRI: Dr. Simon?

16 DR. HAYES: I mean detectable circulating  
17 levels.

18 DR. SIMON: In the analysis both from Immunex  
19 and from you, Jeff, everyone mentioned that if you were on  
20 a DMARD, you dropped off for a month period. Is it assumed  
21 that everybody that was on a previous DMARD was on  
22 methotrexate, or were there other DMARDs that were used in  
23 those circumstances? And if there were, what were they?  
24 That's one question.

25 DR. JEFF SIEGEL: I actually left that off my

1 slide because the slide was looking too busy, but I think  
2 half the patients had been on previous methotrexate, I  
3 think another 20 percent were on hydroxy chloroquine, and I  
4 don't know what percentage were on sulfasalazine. I can't  
5 remember that data.

6 DR. SIMON: But nobody had been on gold or  
7 things like that? We don't use that stuff anymore.

8 DR. JEFF SIEGEL: Very small percentages.

9 DR. SIMON: Very small percentages. And in  
10 your analysis there was no -- because of the way the  
11 response was noted, it didn't appear there was any overlap  
12 with the response from the previous DMARD in combination  
13 with the Enbrel at that point to suggest an early response  
14 that was noted at the beginning?

15 DR. JEFF SIEGEL: So what you're saying is  
16 someone who had been withdrawn from methotrexate --

17 DR. SIMON: Or whatever.

18 DR. JEFF SIEGEL: Were they perhaps more likely  
19 to have an early response? We didn't do that analysis.

20 DR. SIMON: Okay. That's fine.

21 For the second question, I actually need a  
22 primer here on pharmacokinetics, because people threw  
23 around the words "population pharmacokinetics," and I  
24 presume that means you also can do individual  
25 pharmacokinetics, and I'm not entirely sure that all my

1 implications of what that means as it relates to a small  
2 sample population.

3 My take-away message is that I'm worried, I  
4 guess -- and maybe you can help me with this -- I'm worried  
5 that there is drug accumulation, and that we don't  
6 understand why that is, and that the small numbers don't  
7 help us understand that any better, and because we're  
8 already looking at the top dose that's been studied, what  
9 happens when there's dose escalation, which always happens  
10 in the rheumatologic world? So could you help me with this  
11 a little bit, please?

12 DR. GREEN: Population pharmacokinetics is a  
13 very good tool that is a very efficient one to understand  
14 differences among patient populations relative to a model.  
15 So it's very good at using clinical resources efficiently  
16 to know whether renal impairment or other forms of  
17 physiologic change impact on pharmacokinetics. However,  
18 that being said, you need a model to measure your  
19 departure, a reference standard, if you will, and I think  
20 that is the issue: Do we have enough information about  
21 essentially a reference standard so that when a more  
22 sophisticated model like the population pharmacokinetics  
23 one is used, can we detect departures from that model and  
24 interpret them correctly?

25 DR. SIMON: Okay.

1 DR. PETRI: Dr. Tilley, then Dr. Katona.

2 DR. TILLEY: I have two questions. First of  
3 all, Jeff, do you have anymore data on your robustness  
4 analysis?

5 DR. JEFF SIEGEL: You're talking about the  
6 results of the sensitivity analysis?

7 DR. TILLEY: Yes.

8 DR. JEFF SIEGEL: It was all in the briefing  
9 package that I sent you, the actual numbers, but basically,  
10 just to go through it again, there were three scenarios  
11 recategorizing certain patients in a different way to  
12 address possible biases, and in all cases, the proportion  
13 of patients who were responders was similar to not carrying  
14 out that analysis. When all subjects who met prespecified  
15 criteria for lack of efficacy were recategorized as  
16 failures, what you found was that the proportion of placebo  
17 patients who achieved an ACR 20 response fell, and the  
18 proportion of Enbrel-treated patients did not fall very  
19 much. So the numbers were quite similar to the other data.

20 DR. TILLEY: Okay. And then a  
21 biostatistician's question about the pharmacology. The  
22 data that was shown that showed that people, after the drug  
23 was withdrawn, seemed to have a decrease in their  
24 responses, would that suggest that there isn't a build-up  
25 or a carryover, or does that really answer that question?

1 DR. GREEN: I don't know if you can -- my  
2 personal view is, I don't know if you can answer that  
3 question, since we don't know the relationship of serum  
4 concentrations to disease. There's no pharmacodynamic  
5 model that I know of which adequately would explain the  
6 interrelationship of those variables.

7 DR. PETRI: Dr. Katona, then Dr. Brandt.

8 DR. KATONA: I would like to ask two questions,  
9 and the first one is for Dr. Siegel, whether the second  
10 pediatric study will include any children under 4. It's an  
11 important question, because there is a peak between 1 and 3  
12 years of the pauci- and polyarticular JRA, so we would need  
13 to know that data.

14 DR. JEFF SIEGEL: The ongoing trial does not  
15 include any children under 4. This is a question we would  
16 like to get input from the advisory committee about. When  
17 the trial was first being designed and Immunex and the FDA  
18 were undergoing discussions, the question was raised about  
19 whether it should include children under 4, and it was  
20 ultimately decided that this particular study would not,  
21 but we would be very interested in your thoughts later on  
22 about what kind of information you'd like to collect  
23 subsequently.

24 DR. KATONA: My second question is for Dr.  
25 Green. When we talked about pharmacokinetics, we talked

1 about the dosage as well as the half-life influencing the  
2 serum concentration. This is a very different type of  
3 medicine, like when we take a pill and we have a complete  
4 purity of some manufactured chemical. I would be very  
5 interested in some data as far as the purity, the  
6 stability, biological activity, the shelf life, whether  
7 there could be some variables within, like, vial to vial of  
8 Enbrel.

9 DR. GREEN: Perhaps we can have Kathleen Clouse  
10 respond.

11 DR. CLOUSE: All of those parameters are looked  
12 at as part of the --

13 DR. PETRI: I'm sorry, you'll have to move  
14 closer to the microphone.

15 DR. CLOUSE: All the parameters that she  
16 indicated are reviewed as part of the CMC under a complete  
17 manufacturing review, and we do have stability data on the  
18 material. As of right now, commercial materials has  
19 stability studies out to 12 months, and the other  
20 parameters we don't usually discuss at the meeting in open  
21 session, but, yes, all of that is taken into consideration.

22 DR. PETRI: I'm actually going to ask that Dr.  
23 Brandt's question be the last question, because we have  
24 multiple registrants for the open public hearing.

25 Dr. Brandt?

1 DR. BRANDT: A question for Dr. Green.  
2 Realizing the limitations of fitness of the data with  
3 regard to conclusions about half-life and accumulation,  
4 from what we know about the molecule, is there reason to be  
5 concerned or to suspect that the clearance from the blood  
6 or half-life might be related to serum albumin levels or to  
7 activity of the disease, as reflected perhaps by the number  
8 of swollen joints?

9 DR. GREEN: Your question is whether there's a  
10 pharmacokinetic relationship in terms of serum levels to  
11 disease response?

12 DR. BRANDT: Or even a possible one if the data  
13 aren't sufficient to answer that.

14 DR. GREEN: Oh, yes, I think that that's true.  
15 I think the limitation is inherent in pharmacokinetics,  
16 given the state of the art in that science, and that is,  
17 basically you measure from serum concentrations, but what  
18 you're really interested in are tissue concentrations. So  
19 there's a relationship there which we, to some degree,  
20 infer rather than directly measure, and to the extent that  
21 it will be related to amount dose, dosing duration, and  
22 patient-dependent factors, that will influence the levels,  
23 but the dose response, I think, indicates that there is a  
24 response.

25 DR. BRANDT: How about serum albumin levels?

1 DR. GREEN: Serum albumin levels, I don't think  
2 that it's been looked at, but I don't think we'd expect  
3 that that would be involved with Enbrel's pharmacokinetics.  
4 There are, for many biologics, other protein molecules that  
5 they do bind to, but in general albumin is not an important  
6 consideration for large-molecular-weight biological  
7 entities.

8 DR. PETRI: Thank you.

9 For the committee members who have additional  
10 questions, I'm going to ask you to bring them up at the  
11 appropriate points with the discussion questions this  
12 afternoon.

13 I'm going to ask Bill Freas if he could please  
14 introduce the registrants for the open public hearing.

15 DR. FREAS: At this time I have received four  
16 requests to speak during the open public hearing and a  
17 letter to be read into the public record. I will call the  
18 presenters to the microphone in the order in which I  
19 received the requests. The presenters are welcome to use  
20 any microphone they choose. We will limit them to a  
21 presentation time of 5 minutes each, and I will say the  
22 word "time" at the end of that time allotment.

23 The first presenter, if you would come to the  
24 microphone, will be Elizabeth Petersen from Chicago,  
25 Illinois.

1                   Now, while she's going to the microphone, I  
2 will ask all presenters, in the interest of fairness, to  
3 please address any current or previous financial  
4 involvement with any firm upon whose products you wish to  
5 comment. This financial involvement would include travel,  
6 reimbursement for any expenses, owning of stock, or any  
7 affiliation with the firms.

8                   Thank you.

9                   MS. PETERSEN: I am here voluntarily and at my  
10 own expense, and I do have shares in Immunex. My husband  
11 just gave me some shares for my birthday on September 3rd.

12                   (Laughter.)

13                   MS. PETERSEN: And I'm proud to own them. It  
14 would be unwise not to own any.

15                   (Laughter.)

16                   MS. PETERSEN: To my neices, my great-neices,  
17 and to my millions of RA sisters, this is for you.

18                   First, let me indicate that after the 12-week  
19 double-blind study, I learned that I received the 25-  
20 milligram dose. My injection site reaction consisted of a  
21 minor itch that lasted about 5 minutes.

22                   All you people in the panel are so  
23 knowledgeable in the technical and clinical aspects of RA.  
24 I can only tell you about my experience with it. I was  
25 diagnosed with RA at the age of 29. At that time, I was

1 told that there was no cure for it, and that I had to learn  
2 to live with it. After living with RA for 36 years, I  
3 think I've learned to be a better human being, or at least  
4 to be a fighter. I have experienced some very severely  
5 painful short attacks and some less severe, but more  
6 prolonged attacks, but all the while there have also been  
7 the sneak attacks that creep into the joints almost  
8 unnoticed because it's hurting more someplace else, all of  
9 it combining through loss of mobility to make me a prisoner  
10 in my own body.

11 Now, this may sound horrible to some who have  
12 not experienced it, and it is, but there are lessons to be  
13 learned in everything if you look for them. When my hands  
14 were too tender to shake hands with anyone, I learned that  
15 I could hug just about everyone, and hugs are better.

16 I have fought RA first with B12 injections to  
17 alleviate the anemia that came with it, then with a variety  
18 of NSAIDs, some that did nothing and some that made me  
19 violently ill, gold shots for a prolonged time until I  
20 tasted metal, and then prednisone, which made me moon-faced  
21 and depressed, and occasional cortisone shots, which  
22 contributed to bone loss. Finally, when I was not covered  
23 by insurance for the preexisting condition, I did whatever  
24 God inspired me to do, taking aspirin, vitamins, eating  
25 right, and exercising.

1                   Then, just about 3 years ago, by the grace of  
2 God, I wound up participating in a double-blind study for a  
3 new medication. My Bible study group prayed that I would  
4 get into this study, and further prayed that I would  
5 receive the medication and not the placebo. Well, guess  
6 what? The following morning, after the very first  
7 injection, I felt so loose that on our morning walk with  
8 the dog, I was skipping down the alley to show my husband  
9 how well I felt. I had not skipped in years, I guarantee.  
10 I truly felt as if I had been released from prison. I was  
11 so happy, I couldn't stop grinning for a couple of weeks.  
12 I think I was smiling in my sleep. I felt so good, nothing  
13 could even make me angry, and normally I have a short fuse.

14                   With the help of God and that medication, I  
15 sailed through that winter, flying high with no side  
16 effects. When the 12-week study was over, Dr. Reuterman  
17 suggested that I try methotrexate, but I could not convince  
18 myself to take it, for fear of the known side effects, and  
19 since the symptoms were slow to return, I felt I could  
20 manage. After several months, I was invited to participate  
21 in an extended trial of the same medication. This trial  
22 was not blind, and I learned that the name of the  
23 medication was Enbrel. That name, Enbrel, is music to my  
24 ears.

25                   Now, after 2 years of Enbrel -- and I might

1 add, I am overwhelmed at the realization of my good fortune  
2 -- I still have had no adverse effects. The only side  
3 effect that I've noticed is that I seem to be deeply in  
4 love with the entire Immunex Corporation --

5 (Laughter.)

6 MS. PETERSEN: Especially the scientists who  
7 developed Enbrel.

8 Seriously, though, I now have the stamina to  
9 invite two and three of my great-neices at a time for  
10 overnights, and the energy to teach them some of the things  
11 that I've learned over the years, and have fun doing it.

12 Just as I, though, at times have prayed for  
13 death and am now enjoying living, I would like to see  
14 Enbrel become available to millions of other RA sufferers  
15 who may still have a chance to return to productive,  
16 satisfying, and enjoyable lives. Please make it happen for  
17 them, too.

18 DR. FREAS: Thank you very much, Elizabeth.

19 Our next speaker will be Gloria Baswell from  
20 Gadsen, Alabama.

21 MS. BASWELL: First, I want to tell you how  
22 honored I am to be here and to be in the presence of all of  
23 this knowledge. I mean, it's awesome.

24 And I want to tell you the reason I'm here, and  
25 it has nothing to do with Immunex Corporation, other than

1 they developed this miracle drug. That's what I call it,  
2 my miracle. They didn't pay me to come here. I wanted to  
3 come on my own. I discovered on my own, through a press  
4 release on my little computer that I am getting into, that  
5 this was an open-to-the-public meeting, and I couldn't wait  
6 to come and talk to you and tell you just what Enbrel has  
7 done to me.

8 I also didn't come here because I own stock in  
9 Immunex Corporation. I do. I own 70 shares. I bought  
10 those 70 shares because my arthritis was so bad, and I was  
11 on all these current therapies that were not working, and  
12 my jet-ski that I loved, I couldn't hold onto the  
13 handlebars anymore and had to sell it. I stuck the money  
14 away thinking, "Someday I'll buy something good," but as  
15 bad as I was, there was nothing good in my life, and then  
16 Enbrel came along. And when Enbrel came along, after  
17 several months of it, I thought, "Immunex Corporation is  
18 good." I've never bought stock before in my life, but I  
19 believed in this company and I believed in this drug, and I  
20 wanted my little 70 shares, whatever little money I got  
21 from my jet-ski, to go to Immunex Corporation to maybe help  
22 them with their research.

23 So those are the reasons I'm not here, but the  
24 reason I am here is because I want to tell you, I was  
25 terrible before. I used all the current therapies. None

1 of them worked. The NSAIDs, I took every one known to man.  
2 Gold injections, I had a horrendous allergic reaction. I  
3 took methotrexate pills. I vomited and had bloody  
4 diarrhea, acute gastritis. I tried minocycline. I had  
5 some results, but had to discontinue that due to side  
6 effects. One time I was taking 16 pills a day. I had to  
7 keep a notebook on my kitchen counter to keep up with how  
8 many pills to take and when, because I got confused about  
9 the pills. There was too many.

10 I also tried asulfadine, and it didn't work,  
11 and it made me feel awful. I tried the methotrexate  
12 injections, because the pills were so horrible on my  
13 gastrointestinal system. Well, it didn't work, and I may  
14 be one of the ones they were talking about with the  
15 vaginitis. I got it from methotrexate. I didn't get it  
16 from Enbrel. I already was having problems with that, and  
17 that's why I had to stop the methotrexate injections.

18 My doctor and I were trying everything.  
19 Nothing worked. I was getting more destroyed from the  
20 drugs. The RA was still destroying. It was raging,  
21 robbing me of my independence, and no pain pill I ever took  
22 ever touched the pain. When the opportunity came to enter  
23 this Enbrel trial, which at the time was tumor necrosis  
24 factor receptor fusion protein p75, and that's all I knew  
25 about it, I was being maintained on prednisone, with all

1 its ensuing side effects. I had been on prednisone for 2  
2 years and no other drugs, because I couldn't take any other  
3 drugs. I was prediabetic because of the prednisone. I had  
4 high blood pressure. I was like a blimp. I had the moon  
5 face.

6 I've been off prednisone for 1 year, because  
7 I've been in this trial with Enbrel for almost 2 years.  
8 Enbrel is the only thing I use. I don't use anything else,  
9 no NSAIDs, no methotrexate. I'm wonderful. I'm the best  
10 I've ever been. I think I'm even better than I was before  
11 the rheumatoid arthritis --

12 (Laughter.)

13 MS. BASWELL: Because I know what hell is like,  
14 and I know how good it feels to come out of it, and I've  
15 stayed out of it. I don't feel like I even have rheumatoid  
16 arthritis. If I didn't have the damaged joint that the  
17 arthritis did before Enbrel came along, I wouldn't know I  
18 had rheumatoid arthritis.

19 I came here today to ask you to please approve  
20 this drug for me. My damage has stopped, my arthritis has  
21 stopped, and I feel wonderful. And I ask you to approve  
22 this drug for other people who are not as far advanced as I  
23 am, because I understand there are studies going on with  
24 people diagnosed 3 years or less, and that Enbrel has a  
25 possibility of stopping joint damage before it even starts,

1 and that would be another miracle.

2 I just wanted to come here and tell you I don't  
3 have any side effects, I don't have any injection site  
4 reactions. When I take the needle out and I start to wipe  
5 with the alcohol swab, I have to just guess at it, because  
6 I can't even tell where it went. I've had absolutely no  
7 side effects at all, except maybe that well-being part. I  
8 feel like I've got a life back. Before Enbrel came along,  
9 I didn't have a life, and there were lots of times when I  
10 really wished I didn't have a life, period. I mean, I  
11 thought of suicide several times. When you live in this  
12 kind of constant, chronic pain that nothing can touch, it's  
13 depressing, and when you lose everyday things that you take  
14 for granted, like being able to brush your teeth or comb  
15 your hair -- before Enbrel, I couldn't even reach my face.  
16 I couldn't talk on the phone without using a headset,  
17 because I couldn't reach my ears. But I can do that now.  
18 I can do a lot of things now.

19 I also want to ask you to approve Enbrel for  
20 some of my buddies on an arthritis on-line support group.  
21 We don't have one in our area, but I found one on the 'Net,  
22 and a few of them sent some letters, and I'd like to submit  
23 them for the record. They asked me, since they couldn't  
24 come, would I bring their letters and present them to the  
25 FDA board, and they want to tell you why they want Enbrel.

1 They want to tell you the same thing that I want to tell  
2 you, that the current medications, the current therapies  
3 have a lot to be desired. Some of them cause effects that  
4 are worse than the RA.

5 It's my hope and theirs that we can convey to  
6 you what it's almost impossible to convey except to another  
7 arthritis sufferer -- the pain, the debilitation, the  
8 restriction, the frustration, the fear and uncertainty of  
9 RA -- and it is our hope that you will empathize and say  
10 that we are not alone.

11 I would like to thank the scientists and others  
12 at Immunex Corporation, and I'd like to be able to shake  
13 every one of their hands, because I couldn't shake my  
14 doctor's hand the day I went to get the study, but I can  
15 now. I have a really firm handshake.

16 Thank you for hearing me.

17 DR. FREAS: Thank you very much, Gloria, and I  
18 will accept those letters on behalf of FDA, and we'll make  
19 them available through the FOI Office and distribute them.

20 Our next speaker is Margaret Crowley. Margaret  
21 Crowley is from Huntsville, Alabama.

22 MS. CROWLEY: I'm just going to stop right  
23 here, because I don't have very much to say, other than the  
24 fact that I'm not affiliated with anybody. My arthritis  
25 was so bad, I retired. I took early retirement.

1 DR. PETRI: I'm sorry, you're going to need to  
2 speak right into the microphone. Thank you.

3 MS. CROWLEY: I'm sorry, I'm standing on  
4 something over here.

5 I said I'm not affiliated with anybody, Immunex  
6 or anybody else, because I had to take early retirement  
7 because of my rheumatoid arthritis. I came here because I  
8 had heard about the meeting, I have heard about Enbrel, and  
9 I want to know more about what is available and what can be  
10 done and when can I get this.

11 Gloria is my cousin. She has told me so many  
12 wonderful things. I just met Elizabeth. The Internet is  
13 full of people who are telling you what's going on, and  
14 it's just -- I just feel that I have to have this, because  
15 I have so many problems, and I'm not as debilitated as a  
16 lot of people and as Gloria was and as Elizabeth was yet,  
17 but I know it's coming.

18 I know that I am on all of their drugs, the  
19 prednisone, the methotrexate, the Indocin. I'm having to  
20 take hormones, I'm taking calcium, I'm taking vitamins,  
21 trying to eliminate and at least help some of the side  
22 effects from all of these drugs that I'm having to take.  
23 So what I need is something that might give me a little bit  
24 more hope.

25 DR. FREAS: Thank you very much, Margaret.

1           Our next speaker is Noreen Walker. Noreen is a  
2 representative of the Arthritis Foundation.

3           MS. WALKER: Good afternoon, and the Arthritis  
4 Foundation thanks you for the opportunity to come before  
5 you today. I'm surprised at the number of people here;  
6 however, I am very pleased to deliver my message.

7           I am a volunteer with the Arthritis Foundation.  
8 I've served locally on the Maryland Chapter board for a  
9 number of years. I have interfaced with many different  
10 people that have arthritis, that are arthritis health care  
11 professionals, researchers, people that are caring for  
12 individuals that have arthritis, as well as other people  
13 that are just interested in fighting for our cause.

14           The mission of the Arthritis Foundation is two-  
15 fold. The first part is to support research to determine  
16 the cause of and the cure for the over 100 different types  
17 of arthritis. The second part of the mission is to improve  
18 the quality of life for people that have arthritis.

19           In addition to being an Arthritis Foundation  
20 volunteer, I also have rheumatoid arthritis. I was  
21 diagnosed 20 years ago as a freshman entering college at  
22 the University of Maryland. At that time, entering a  
23 program in the College of Engineering, which was very  
24 challenging, I had tremendous goals, tremendous aspirations  
25 for the future, and the message that I got from the

1 rheumatologists and the literature that I had read at the  
2 time indicated that it was not unusual for someone with  
3 rheumatoid arthritis to be disabled within 5 years. Well,  
4 that didn't really fit into my program for what I wanted to  
5 do.

6 Over the years, I was very fortunate to have  
7 the benefit of being treated through teaching hospitals,  
8 first through Walter Reed Army Medical Center, and then  
9 later on through Johns Hopkins University. The treatment  
10 program included a team approach: rheumatologists,  
11 orthopedic surgeons, occupational therapists, physical  
12 therapists. All of these people worked together with me so  
13 that I could improve the quality of life and have a  
14 successful and satisfying career.

15 During that period, I was treated with a number  
16 of different medications, including the NSAIDs, the DMARDs,  
17 and all the other different types of arthritis drugs that  
18 were on the market.

19 I am not a participant in the Enbrel study. I  
20 am not a representative in any way of Immunex. I don't  
21 have stock in Immunex at all. I forgot to mention that  
22 earlier on.

23 Through working with the team approach, I have  
24 been able to control the arthritis that I have, and I'm  
25 diagnosed with a moderate form of arthritis; not minor

1 aches and pains, but a moderate form. I have had the  
2 opportunity to be a success in my career, to be recognized  
3 by my peers as a success; however, I do take a number of  
4 different medicines. I have been diagnosed, because of the  
5 side effects, with other maladies in addition to rheumatoid  
6 arthritis, some of which are associated with simply having  
7 rheumatoid arthritis and others because of the long-term  
8 effects of the drugs, and have had to take supplements, et  
9 cetera, for that treatment.

10 The Arthritis Foundation would like to support  
11 the continued study of Enbrel, and to suggest to widen and  
12 expand the field of study that's been done at this time, to  
13 increase the number of patients, and to discern the number  
14 and amount of side effects that may be complicated with  
15 rheumatoid arthritis patients that have varying other  
16 complications in their lives.

17 I'd be happy to answer any questions or meet  
18 with anyone after. Thank you for the opportunity to speak  
19 on behalf of the Arthritis Foundation.

20 DR. FREAS: Thank you, Noreen.

21 I would now like to read into the public record  
22 the letter that was submitted in response to the Federal  
23 Register Notice.

24 "My name is Judy Shiffers. I'm a 53-year-old  
25 woman who has been suffering from rheumatoid arthritis for

1 11 years. Before the onset of my illness, I was a vibrant  
2 person and active cellist, having performed in the Israel  
3 Chamber Orchestra, with the Baltimore Symphony and various  
4 and sundry other groups. My career as a performing  
5 musician is over, though I am still able to teach.

6 "Aside from the fact that I can no longer play  
7 the cello, my day-to-day existence is severely restricted.  
8 I spend a good part of the day in bed waiting for the  
9 rather high dosage of steroids I am taking to give me some  
10 relief. In between, I take Tylenol for the pain. At best,  
11 I am able to "have a life" about 3 or 4 hours per day.  
12 Otherwise, I am pretty much confined to home.

13 "I have taken most all of the conventional  
14 drugs given for the treatment of rheumatoid arthritis.  
15 Either I experienced an adverse reaction or the drug was  
16 not effective. Over the years, I have seen the  
17 deterioration of my health. I am rather anemic. A few  
18 months ago I developed pleurisy, and then was hospitalized  
19 for pericarditis.

20 "At the moment, I am taking sulfasalazine and  
21 plaquenil. To this combination, methotrexate will be  
22 added. In addition, I am on prednisone. Even with all of  
23 these drugs, I am barely functional. I have been on  
24 plaquenil and methotrexate before, and despite all of these  
25 medications, my condition has worsened. My rheumatologist

1 believes that of all the new drugs about to appear on the  
2 market, Enbrel might offer the best hope for me.

3 "I respect the regulatory process and  
4 understand the need for assuring the safety of any  
5 medication. However, I also know firsthand how  
6 deteriorating with a chronic illness affects one's life and  
7 outlook. A few weeks or months on the regulatory calendar  
8 may seem insignificant, but we who live in daily pain can  
9 only hope that concern for the public's welfare does not  
10 turn into unnecessary delays and disregard for the very  
11 ones you are trying to help.

12 "I can only ask that if Enbrel has passed all  
13 of its clinical trials, that it be released to the public  
14 in an expedient way. Many of us suffer and await any news  
15 of something that can alleviate our condition. I know  
16 Enbrel is not a cure, but if it can improve my quality of  
17 life, my physician needs to be able to prescribe it as soon  
18 as possible.

19 "In light of the fact that the procedure that  
20 the FDA needs to follow may take some weeks or months, I am  
21 asking for permission to receive Enbrel out of humanitarian  
22 reasons, as a compassionate gesture, as soon as possible.

23 "Thank you very much for taking time to hear my  
24 letter." Signed, Judith Shiffers.

25 DR. PETRI: The committee thanks all the

1 participants in the open hearing for their heartfelt pleas  
2 for new treatments for rheumatoid arthritis. That's  
3 obviously the goal of all of us here today.

4 We will reconvene at 1:30. Thank you.

5 (Whereupon, at 12:38 p.m., the meeting was  
6 recessed for lunch, to reconvene at 1:30 p.m.)

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AFTERNOON SESSION

(1:35 p.m.)

1  
2 DR. PETRI: This afternoon we're going to be  
3 discussing the questions. Several of the questions have a  
4 preamble. I'm going to ask you to read those preambles  
5 yourself, and I will read the parts in bold.

6 I want to remind everyone that I invite  
7 discussion from everyone in the room, including, of course,  
8 Immunex, their invited consultants, of course our committee  
9 members, and also experts in the audience.

10 The first question we're asked to discuss this  
11 afternoon is, "Please discuss the risk of infection  
12 associated with Enbrel use. What information relating to  
13 this risk should be included in the package insert if the  
14 product is approved? Should the sponsor be encouraged to  
15 conduct additional studies pre- or, if approved,  
16 postmarketing to better characterize the infection-related  
17 adverse events? If so, what types of studies should be  
18 considered?"

19 I wanted to start by reminding all of us that  
20 the infection rates were not increased with Enbrel, and I'd  
21 like to ask Immunex if they could review with us their data  
22 on immunocompetence. There were several questions this  
23 morning about the immunocompetence data.

24 DR. HAYES: I'm going to ask Dr. Michael Widmer  
25 from our preclinical group to discuss the assays that were

1 performed.

2 DR. WIDMER: The primary test for  
3 immunocompetence was delayed-type hypersensitivity skin  
4 testing, in which patients were tested for skin test  
5 reactions to three antigens. There were 49 patients  
6 evaluated in the 16.0009 trial. All patients exhibiting  
7 positive responses to a given antigen maintained those  
8 responses throughout the treatment period, throughout the  
9 trial, and the testing times were prior to therapy  
10 initiation, at 3 months, and at 6 months.

11 At this study site, there was also an  
12 evaluation of lymphocyte subtypes by flow cytometry. As  
13 reflected in the DTH results, the lymphocyte subtypes were  
14 not found to change through the course of the trial. Those  
15 lymphocytes were also examined functionally by a  
16 lymphoproliferation assay involving stimuli staph  
17 enterotoxin B, concanavalin A, and phytohemagglutinin, all  
18 T-cell stimulators.

19 Neutrophil function was also assessed.  
20 Neutrophils were assessed for oxidant generation,  
21 phagocytosis, and microbicidal activity. Once again,  
22 neutrophils from the patients were found to be functionally  
23 active both before and after treatment, and quantitative  
24 serum immunoglobulin determinations were made on the  
25 immunoglobulin subtypes that you see listed here. Again,

1 there was no change evident in quantitative levels of serum  
2 immunoglobulin.

3 DR. PETRI: Specifically, though, there's been  
4 no post-vaccination antibody titer study.

5 DR. HAYES: No, we have not. As I alluded to  
6 this morning, there have been about 100 patients who have  
7 received various vaccines during these trials, because,  
8 again, they were not contraindicated or prohibited, but we  
9 did not look at levels to see whether or not these patients  
10 have responded or not.

11 DR. PETRI: I wanted to ask the committee  
12 members who had had concerns this morning if they could  
13 further address this issue. Let me start with Dr.  
14 Abramson.

15 DR. ABRAMSON: I don't think I have any real  
16 concerns. The only point I was making in my question about  
17 neutrophil function is that unless the cells were  
18 stimulated with TNF prior to whatever function you were  
19 assessing, I'm not sure that you can call the cell function  
20 normal. And I wasn't sure in the answer to my question  
21 this morning whether these were just stimulated with chemo  
22 attractants or killing of bacteria or when first at a TNF,  
23 which normally doesn't have much of an effect by itself,  
24 and then you came in with the test you were then going to  
25 do.

1 DR. WIDMER: Right. The oxidant production  
2 assays were done by coating the wells of microtiter plates  
3 with immunoglobulin in the presence or absence of TNF. So  
4 the assessment was made as if TNF would be inducing  
5 function there.

6 DR. PETRI: Let me ask Dr. Frieri if she has  
7 additional concerns from her discussion this morning.

8 DR. FRIERI: Yes. In the packet, it said  
9 streptococcal, but it is staph aureus choanae, I believe.  
10 EBV was not used as a stimulant. And also, in the flow  
11 cytometric data, which shows that the CD-19 was changed as  
12 well as one of the other markers for B-cell phenotypes,  
13 what about B-cell function, such as a plaque assay?

14 DR. PETRI: Can I ask Immunex to respond to  
15 that? Dr. Hayes?

16 DR. HAYES: As far as I know, the investigator  
17 who was doing these studies has not done any further  
18 studies than what we have stated. We only have a response  
19 to an infection with a normal antibody response in one  
20 pediatric patient who developed totally normal antibody  
21 levels following VCV. It's the only patient that we have  
22 studied. The second patient, we are assessing that, but we  
23 do not have the data yet.

24 DR. PETRI: Dr. Yocum, did you have a question  
25 or a comment?

1 DR. YOCUM: I guess I have the same concerns  
2 that there's a relative lack of B-cell function here, which  
3 TNF appears to be important in regulating B-cells. And Dr.  
4 Frieri's comment about the CD-19 population, I assume that  
5 rheumatoid factor did not go up or down significantly with  
6 these other autoantibodies, and did they look at the IgM  
7 and IgG rheumatoid factor?

8 DR. PETRI: Dr. Hayes or Dr. Garrison, can you  
9 respond?

10 DR. HAYES: There was no significant change in  
11 rheumatoid factor in any of the patients on our trials. In  
12 0009 there was a negligible positive effect in reducing it.  
13 In 0014 the opposite occurred, and we did not look at  
14 subsets.

15 DR. PETRI: To address the questions very  
16 specifically, I wanted to ask the panel, what information  
17 on risk of infection should be included in the package  
18 insert? And I'd like to also have the panel, as they think  
19 about this, consider the issue of vaccination. Should both  
20 adults and children be completely up to date with  
21 vaccinations before starting?

22 Dr. Silverman, do you want to start the  
23 discussion?

24 DR. SILVERMAN: I have just a couple of  
25 comments, too. Was there a power analysis done? Because

1 some of these numbers are very small, and this is a  
2 negative -- regarding the immune function. Certainly, the  
3 facts analysis says between 7 and 18 patients, and at most  
4 it's between 25 patients, and you have to get fairly  
5 significant changes. So I wouldn't be overly confident  
6 without certainly looking at confidence intervals and power  
7 analysis of the immune function.

8 Which brings me into my next concern, and that  
9 was two patients with aseptic meningitis secondary to  
10 varicella infection. It's not a common occurrence in  
11 pediatrics, when there's only 69 patients entered into a  
12 study, without knowing off the top of my head, which I  
13 don't know, how common it is, but that seems outrageously  
14 high.

15 Which then leads to my next concern, and that  
16 was with the septic arthritis and polymicrobial, and not to  
17 say that this -- who then went on to die. Not to say that  
18 this drug is any better or worse than current drugs on the  
19 market, but I certainly would have caution in the use in  
20 the presence of varicella, particularly in children, and  
21 the guidelines I would think would be very similar to the  
22 methotrexate guidelines both for infection as well as  
23 chicken pox in children.

24 DR. PETRI: Because there are so many adult  
25 rheumatologists on this panel, could you please just state

1 specifically what you would want a child to have received  
2 in terms of vaccinations before receiving Enbrel?

3 DR. SILVERMAN: Currently chicken pox is not on  
4 the market. The child would have to be up to date, which  
5 is reasonable on most children, particularly as over the  
6 age of 4 should be. The recommendation we have for  
7 methotrexate would be after an immediate chicken pox  
8 contact, a direct contact, we would hold the medication.  
9 Our personal preference, it would be nice to have an  
10 indication that titers would be known prior to beginning on  
11 the medication, and at the face of varicella in fact, we  
12 hold the medication for methotrexate and give them D-zig.  
13 So on a close contact, then I would think to be prudent,  
14 one would want that, and, again, the indication for any  
15 serious infection requiring hospitalization, to hold the  
16 medication.

17 DR. PETRI: Dr. Katona, did you want to add  
18 anything to this?

19 DR. KATONA: I think the immunization, what I  
20 would worry the most about with the live virus is polio,  
21 and I definitely would put in the label that I would not  
22 recommend anyone to get any polio immunization with the  
23 wide variety of vaccines. And at the same time, until we  
24 have the studies about age 4, by that time most of the  
25 children have got their immunizations, and I think that's

1 unreal to say that you're not going to start the drug,  
2 first you're going to immunize the children. These are the  
3 children who have an active disease, and we're usually very  
4 careful what type of immune stimulus we give the children,  
5 so that's usually not when we're giving out immunizations  
6 that they are the most active.

7           So that's kind of an -- the question, I think,  
8 theoretically is an interesting one, but practicality-wise  
9 we usually calm the disease down first, and then we give  
10 the immunizations. But I think the most important is that  
11 we really need some data. I think even the ones which are  
12 not live viral vaccines is something that we really need to  
13 collect some data, and until we know anything more,  
14 definitely no live vaccines and the precautions that Dr.  
15 Silverman said.

16           DR. PETRI: Dr. Hayes, you had a comment?

17           DR. HAYES: Yes. I would like to put forward  
18 some clarification of these two cases of children with  
19 varicella. As a pediatrician, I'm not sure I would have  
20 called either of these children having any kind of aseptic  
21 meningitis.

22           The first child was a child who developed  
23 chicken pox, and his lesions were scabbing over. He  
24 developed some headache and some vomiting and began having  
25 parasthesias in his hand. This is the child who had

1       subluxation of C1,2, and that was the cause of his  
2       neurologic dysfunction. He did have an LP done, which  
3       showed about 30 lymphocytes. He recovered from his  
4       varicella completely normally, had his subluxation  
5       corrected, his neurologic symptoms disappeared, and the  
6       patient is the patient who developed a totally normal  
7       antibody titer to varicella when it was measured.

8                 The second case is a child who also developed  
9       chicken pox on Enbrel. The child, on the fourth day, when  
10      the lesions were scabbing over, also developed headache and  
11      some fever and some vomiting, had no meningeal signs at  
12      all, and was called an aseptic meningitis. That child 4  
13      days later was entirely normal and recovered from chicken  
14      pox and continues on Enbrel.

15                So I think that we're not denying that these  
16      children did have headache and vomiting, but I think as a  
17      pediatrician, I certainly, in the absence of this child's  
18      neurologic symptoms, would probably not have tapped either  
19      of these children, and I'd like Dr. Giannini to comment on  
20      this. He's our pediatric consultant. Both of these  
21      children recovered from varicella in the expected period of  
22      time.

23                DR. PETRI: Dr. Giannini, can I ask you also to  
24      address this concern the panel has raised about holding  
25      live vaccines?

1 DR. GIANNINI: The only thing that I can add is  
2 that none of our children on the trial received live  
3 vaccines during the study. So I must leave it rest and say  
4 we just don't have any data. I can't add anymore than  
5 that.

6 DR. SILVERMAN: If I can just comment on Dr.  
7 Hayes, in the presence of 30 white cells, I find it hard to  
8 deny the diagnosis of aseptic meningitis. I personally  
9 could not justify that putting it to a sublucation of C1,2.  
10 I don't understand the mechanism allowing for 30 white  
11 cells. I understand we may not have done the LP, and maybe  
12 more children do have headaches and vomiting than we  
13 suspect.

14 However, having said that, chicken pox usually  
15 doesn't "get better" and then you get the headache, and  
16 those children must be suspected of aseptic meningitis, and  
17 I stay by my concern.

18 DR. PETRI: Dr. Simon?

19 DR. SIMON: May I ask the chair, in asking that  
20 question, is there an inherent acceptance of the data that  
21 we have, which is non-existent, about the potential risk  
22 for children or anyone receiving live vaccine as a  
23 preparation to prepare a response to exposure? It seems to  
24 me that we can't answer that question without actually  
25 seeing more data accumulated, and to make recommendations

1 with the dearth of information that we have makes me very,  
2 very uncomfortable.

3 DR. PETRI: The way these questions are ordered  
4 is perhaps backwards, but we were asked first to suggest  
5 information that should be in the package insert, and we're  
6 going to be asked next to suggest additional studies.

7 DR. SIMON: Well, maybe I could just make the  
8 comment that since we were asked that, I think no  
9 information should be in the package insert, because I  
10 don't think there is any data that would allow us to use  
11 these drugs safely in children. Not enough children have  
12 been studied. These studies are still ongoing, and I think  
13 it's way too premature to be able to consider the  
14 possibility of giving this to children, however important  
15 it is to make them feel better.

16 DR. PETRI: Let's not jump ahead, because we  
17 have the whole question about children and the pediatric  
18 rule. So let's try to focus on infection risk in this  
19 question; otherwise, I'm afraid we will get off base.

20 Dr. White?

21 DR. WHITE: My view of the infection data is  
22 that I am swayed by the infection rate per year, and I have  
23 not been concerned that there's an increased rate of  
24 infection per patient per year, and I think those are the  
25 data that I saw. I do also, though, have some concern

1 about the severity of infections once they do occur, which  
2 is a little different issue, and I think that we don't have  
3 those data to make adequate decisions about what to say or  
4 not say.

5 DR. PETRI: Dr. Felson?

6 DR. FELSON: I think we have to be mindful of  
7 the fact that there's evidently a sepsis trial out there  
8 that shows that people who got this had more deaths than  
9 people who didn't --

10 DR. SIMON: David, can you speak up, please?

11 DR. FELSON: I think that the countervailing  
12 piece of evidence is the sepsis trial, and I think that's  
13 got to be foremost in our minds here, and I think there are  
14 other concerns that perhaps might relate to accumulation of  
15 the drug based on the absence of PK data that shouldn't  
16 make us feel real comfortable that this is likely to be  
17 safe over long periods of time and not cause infection,  
18 given its mechanisms of action, which might -- Steve  
19 pointed out earlier, and I think David pointed out a while  
20 ago -- might well lead to some kind of immunocompromised  
21 inability to fight off infection.

22 I'm not sure that there's any data right now to  
23 say anything. I'm not impressed that there's enough long-  
24 term experience with this agent. There are a lot of areas,  
25 I think, as we approach this where we're just not going to

1 have enough data to answer the question. We can speculate  
2 all we want.

3 I think what we're going to need to have here  
4 and in some of the other long-term side effect issues we're  
5 talking about is Phase IV-type information. I think that's  
6 part of this question, and I think what's needed is a  
7 follow-up study with treated patients over time, comparing  
8 them to untreated similarly derived patients to see if  
9 there's any increased risk of infection based on rates  
10 already determined in the clinical trial, definitions  
11 already arrived at by the trial data, and one could power  
12 that kind of observational study pretty easily, and I think  
13 that's probably what's needed here.

14 I think if you want to throw vaccines into that  
15 mix, that's fine, but I'm not comfortable that there's  
16 enough data to say one way or another. I think there's not  
17 necessarily enough data to reassure us that this isn't  
18 going to be a problem over the long term.

19 DR. PETRI: Dr. Yocum, then Dr. Frieri, then  
20 Dr. Hayes.

21 DR. YOCUM: David, in the study that you would  
22 power, would you then include higher dosage? Because, you  
23 know, Lee has brought up questions earlier about -- and I  
24 think Jeff's presentation -- whether we really plateaued or  
25 not on this, and given that rheumatologists have a penchant

1 for giving more of anything, because if this works twice as  
2 much, it will be better, is that a concern of yours?

3 DR. FELSON: I think that's a different issue,  
4 David. I would study it as used. I mean, I would do an  
5 observational study of its use. It's going to be used,  
6 it's probably going to be widely used, let's look at people  
7 who get it and see how many get serious infections, mild  
8 infections, hospitalized infections, and compare those to  
9 similarly derived patients from similar practices in  
10 similar locations who aren't treated with this and get a  
11 relative risk of infection.

12 DR. PETRI: Dr. Frieri?

13 DR. FRIERI: I was wondering if the child with  
14 the aseptic meningitis was on a non-steroidal and on  
15 steroids, both of those. We know that even inhaled  
16 steroids in high dose can be slightly a problem with  
17 varicella. So those were my two concerns.

18 DR. HAYES: One of the patients was on Indocin  
19 and not on steroid, and the other was on neither.

20 DR. PETRI: Dr. Tilley?

21 DR. TILLEY: I just wanted to point out in  
22 this, I think one of the things we're struggling with is  
23 the person-years analysis versus the denominator, which is  
24 the number of patients, and I think the limiting factor  
25 here has been the fact that the patients on the placebo

1 were not followed to the end of the trial. Their follow-up  
2 stopped when the drug stopped. If they had been followed  
3 to the end of the trial, we would have had a different kind  
4 of rate to compare, but in this case I think the approach  
5 that the FDA took, which is the conservative approach,  
6 which is assuming that no infections occurred in the  
7 placebo group that weren't recorded, that's sort of the  
8 upper bound for me on what the difference might be.

9 So in the absence of data, I don't feel as  
10 comfortable taking this person-years approach.

11 DR. JAY SIEGEL: Let me just comment on that,  
12 because I think that both approaches are appropriate  
13 approaches, and they get at different aspects of trying to  
14 answer a question for which there are not really the  
15 optimal data to answer, which would be with complete  
16 follow-up data on placebo or not.

17 It's my understanding that the design of the  
18 trial, the reason for the planned dropout of lack of  
19 efficacy is that it was felt for pragmatic reasons, in  
20 terms of encouraging patients to enroll, possibly ethical  
21 reasons as well, that it was advisable to have a design  
22 with a definitive endpoint based on lack of efficacy so  
23 that patients who did drop out would have met the primary  
24 endpoint of the study, and then could be even prior to that  
25 point, at the time of enrollment, offered the opportunity

1 at some point to cross over to open-label trial.

2 I can't speak to the conditions of this trial,  
3 but sometimes that sort of design is quite necessary and  
4 appropriate to ensure adequate enrollment and an  
5 appropriate patient management. However, it does leave you  
6 with a deficient patient database. The correction by  
7 looking at number of patient-years exposure is an  
8 informative one and an interesting one; however, it, as any  
9 analysis, rests on certain assumptions, and I think Dr.  
10 Tilley pointed out the conservative assumption in just  
11 looking at the raw numbers, but there's an assumption in  
12 looking at infections over time that there's a relatively  
13 stable rate of these events occurring over time, and that  
14 although one patient population was followed mostly for 2  
15 months from enrollment and the other mostly for 6 months,  
16 or whatever the numbers are, that those are comparable  
17 periods, that there isn't a likelihood in one arm or the  
18 other or both for either higher rates early on, then  
19 lowering, or lower rates early on, then increasing, both of  
20 which can be observed in clinical trials.

21 So one needs to look at -- I think it's  
22 appropriate to look at the data both ways in a sense that  
23 they form bounds or different approaches to trying to  
24 address the question.

25 DR. PETRI: Dr. Hayes, did you have additional

1 comments?

2 DR. HAYES: Yes. I was going to address Dr.  
3 White's comment about the severity of infection, and I  
4 would like Dr. Jim Lui from Torrence, California, to  
5 address this now.

6 DR. LUI: I think we're all concerned about the  
7 severity of infection, and I'd like to discuss the  
8 specifics of the three cases that were brought up by Dr.  
9 Jeffrey Siegel. So if I could have that first slide that  
10 showed the death from staphylococcal sepsis, I think if we  
11 go over the individual details of this case from a clinical  
12 point of view, you will understand that the outcome was not  
13 unexpected.

14 This is a 54-year-old woman who had been on  
15 Enbrel for almost a year. She had had rheumatoid arthritis  
16 for 14 years. She had high titers of rheumatoid factor,  
17 and four total joints already had been placed, in her right  
18 shoulder, in her hip, and in both knees. She came to have  
19 surgery on her left shoulder to open up a frozen shoulder,  
20 and at that time there was a wound infection following that  
21 required two surgical debridement procedures, following  
22 which the left shoulder had to be opened and a fistula had  
23 to be closed as the rotator cuff was repaired.

24 Now, with that procedure, she had had 33 days  
25 of an antibiotic for a staphylococcal infection, because

1 staph had been identified in that procedure. Seven months  
2 later she awoke with right knee pain, and the pain was  
3 severe enough that she -- and that was in the site of a  
4 prior prosthesis. The pain was severe enough that she  
5 called her physician, met her local physician, who inferred  
6 that this was a flare of her rheumatoid arthritis and  
7 increased her prednisone from 10 milligrams, her chronic  
8 dose, to 40 milligrams a day.

9 She went home for 3 days, and then 3 days later  
10 showed up at the emergency room in respiratory distress.  
11 Obviously, septicemic, she had multiple joints now  
12 involved, and there were skin lesions that were noted. So  
13 she had a polyarthrititis, a neurodermatitis, and she was in  
14 respiratory distress to the extent that they did a VQ scan  
15 to actually look for a pulmonary embolus, but no therapy  
16 was started.

17 The following day, because of the series of  
18 blood tests that had occurred, and because the blood  
19 culture returned with the staph aureus in the blood  
20 culture, the rheumatologist was summoned, the  
21 rheumatologist started the patient on nafcillin and on  
22 vancomycin, but the patient had crashed by that time. At  
23 the same time that was seen that following day, the patient  
24 was admitted to the ICU, intubated, and stayed in an  
25 intubated state for the rest of her time.

1           So though vancomycin and nafcillin were  
2 started, I think her course had already been declared. She  
3 was septicemic in respiratory distress, she had multiple  
4 joints involved that were subsequently tapped and  
5 identified as showing staph aureus, and she never recovered  
6 again so that she could escape from the intubation, and her  
7 family decided after a period of a week, though she was on  
8 appropriate antibiotics and her course was declared, to  
9 withdraw support, and she died.

10           So I think looking at the clinical picture of  
11 that patient, who had all these risk factors for infection,  
12 developed an infection that was missed, and then the  
13 following day -- for 3 days, and then came in in a  
14 septicemic state, declared her course. That's the first  
15 case.

16           DR. PETRI: Jim, I'm actually going to  
17 interrupt, because I don't think we need to review the  
18 individual cases. I think Dr. Felson's point was that we  
19 don't have enough data to reach any conclusions, but I  
20 thank you for summarizing that awful, awful patient  
21 history.

22           Dr. Brandt?

23           DR. BRANDT: I do feel that I wish there were  
24 more data on this to help clarify that, but that feeling of  
25 discomfort is compounded by the fact that we don't have

1 enough PK data. Do such patients -- for example, David  
2 Yocum or somebody raised the possibility of rheumatoid  
3 factor complexing. What do we know in terms of clearance  
4 in more patients? Is this the kind of person who might  
5 have had four times more agent than other patients? I  
6 think we can bemoan the fact that we don't have it today,  
7 we have to move on, but I think I would simply say that  
8 those are the kinds of data that we would like to see in  
9 the future.

10 DR. HAYES: We actually do have data, if you'd  
11 like to see it, on the blood levels in the medically  
12 important infections and cancer.

13 DR. PETRI: On the serious infections you have  
14 blood levels?

15 DR. HAYES: Yes.

16 DR. PETRI: Yes, why don't you show us.

17 DR. HAYES: This is Dr. Yung, who is a  
18 pharmacokineticist from Globamax, who has been reviewing  
19 our pharmacokinetic data.

20 DR. YUNG: What I'd like to quickly do is to  
21 cover some of the issues on the efficacy and safety in  
22 terms of blood levels. I can go into the issues and  
23 clarifications in terms of clearance if you want me to, but  
24 I won't do that quite yet.

25 This is a slide where we actually looked at

1 patients who had serious AEs and their blood levels versus  
2 patients without serious AEs and their blood levels. So  
3 without the AEs -- I shouldn't say serious, just AEs,  
4 infections and cancer. Without the AEs, you can see on  
5 your right-hand side the concentration is comparable to  
6 with AE. There does not appear to be any difference among  
7 the two groups.

8 DR. PETRI: But can you show us for just  
9 infections?

10 DR. YUNG: You want infections without the  
11 cancer? We have very few cancer patients in here anyway,  
12 but this is the infections versus blood levels. The  
13 concentrations on the left, the time and the day in terms  
14 of drawing the samples, and we have two groups here. The  
15 ones with the circles, which are kind of hard to see, but  
16 they're there -- they're yellow -- those are patients with  
17 severe infections or cancer, and the controls are the  
18 triangles, which are white. As you can see, there is no  
19 distinction between the patients with severe infections in  
20 terms of their concentrations and the patients who are  
21 controls, who have no infections.

22 DR. PETRI: Thank you.

23 Dr. Hess?

24 DR. HESS: We saw some very interesting data,  
25 though not absolutely complete, on the immunocompetence

1 work-up in 49 patients. I wondered if there were any  
2 studies done in those who had the infections of what  
3 exactly was their overall immunocompetence state at that  
4 time.

5 DR. HAYES: No, we did not look at the  
6 patients.

7 DR. PETRI: Let's try to pull together where we  
8 are. In terms of the information about infection risk to  
9 be included in the package insert, I think the overriding  
10 impression that I've received, listening to all the  
11 comments, is that we have insufficient data, with the one  
12 caveat about the live vaccines, and that was raised for the  
13 pediatric population.

14 Let me ask Dr. Abramson, should that be a  
15 concern in our adult population as well?

16 DR. ABRAMSON: In terms of the vaccines  
17 themselves? I'm not particularly more of an expert on  
18 that, but I would think that some of the same issues would  
19 pertain in the adult population.

20 DR. PETRI: Let me ask Dr. Jeff Siegel, is that  
21 sufficient for the FDA's concerns about that first  
22 question?

23 DR. WEISS: Yes. We're just trying to get a  
24 handle on what to convey in terms of how much is not known  
25 with respect to chronic use, and I think we're getting the

1 sense that we're going to --

2 DR. PETRI: I think our answer to the next  
3 question will be more apropos. So the next question is,  
4 what additional studies -- I'm sorry. Dr. Abramson?

5 DR. ABRAMSON: I need a clarification, because  
6 I don't think we have enough information to say that it's  
7 safe, but I'm wondering, our other immunosuppressant drugs  
8 -- let's say methotrexate -- in the package insert, I've  
9 frankly forgotten, do we caution against using it in people  
10 who have concomitant bacterial infections, serious  
11 infections? Is there any statement about the possibility?  
12 Because I don't think we have enough to be assured. I  
13 think there's still some concern that there may be a risk  
14 of infection, particularly based on the sepsis data in  
15 people who develop infections on it, where in most  
16 instances we will discontinue methotrexate, as an example,  
17 in the case of an organ infection.

18 So I don't -- the question is, we should do no  
19 less, in my view, at this point, but I'm not --

20 DR. JAY SIEGEL: I can't speak to methotrexate  
21 in particular, but we certainly do, can, and have labeled  
22 -- where there are theoretical concerns and there are  
23 inadequate data to address them, we certainly can put in  
24 the labeling that because of the class of the compound or  
25 mechanism of action, there are the theoretical concerns,

1 and potentially could include cautions about those concerns  
2 and even about discontinuing in the face of vaccination or  
3 serious infection.

4 DR. PETRI: Dr. Hayes, then Dr. Katona.

5 DR. HAYES: If you remember, in my closing  
6 remarks today, I did state that even with the data we have,  
7 that Immunex feels it's prudent to put in the package  
8 insert that any patient with serious infection or impending  
9 sepsis syndrome should have the drug discontinued.

10 DR. PETRI: Dr. Katona, and then Dr. Luthra.

11 DR. KATONA: And I think this is back again to  
12 the way Dr. Hayes finished up her talk this morning, that  
13 Immunex is very committed for long-term follow-up. I think  
14 we really would like to see some additional data,  
15 especially on the specific immune responses. That would be  
16 something very important both for the adults as well as for  
17 the pediatric population on vaccines.

18 DR. PETRI: Dr. Luthra?

19 DR. LUTHRA: Michelle, I was just going to make  
20 a comment about the use of live vaccines for adults. Even  
21 though you're not using them directly in these patients,  
22 these patients may be exposed to children or grandchildren  
23 who have received a live vaccine, and I think there should  
24 be some protection of these patients from them.

25 DR. PETRI: Thank you. That's very important.

1 Dr. Weinblatt?

2 DR. WEINBLATT: I'd like to make a comment  
3 about methotrexate with regard to rheumatoid arthritis. It  
4 was in 1988 that the U.S. Food and Drug Administration  
5 approved methotrexate for the therapy of rheumatoid  
6 arthritis on the basis of two controlled trials, one of 35  
7 patients, which is our study from the Brigham, which was a  
8 24-week crossover study, and one of 189 patients, an 18-  
9 week study, with no long-term data available. The package  
10 insert for methotrexate with regard to rheumatoid arthritis  
11 strictly defines the clinical experience and safety data  
12 with regard to methotrexate based on those trials. It is a  
13 standard of practice with regard to methotrexate, even in  
14 the adult population, since there's no available data, to  
15 avoid the use of live vaccines, and I think this is based  
16 upon the pediatric experience with higher doses of  
17 corticosteroids in that experience, and I think many of us  
18 would be reluctant to do the clinical trial to expose  
19 patients to live vaccines in that setting.

20 DR. PETRI: Thank you.

21 Dr. Silverman?

22 DR. SILVERMAN: Just one final comment. If we  
23 are -- as it reads, "if approved," I would like to see some  
24 comment about the potential, particularly in the face of  
25 corticosteroids, as these patients had, for varicella, some

1 comment regarding its use in the face of a contact of  
2 varicella and active varicella.

3 DR. PETRI: That point's taken.

4 I'd like the people who had suggestions for  
5 additional studies to please help summarize them at this  
6 point.

7 Let me start with Dr. Felson, if you could  
8 summarize the study that you had suggested.

9 DR. FELSON: Well, I think it's a Phase IV  
10 study. It needs to be a study of people on this  
11 medication. You've got people already, you've got a cohort  
12 of people being followed. I think that needs to be coupled  
13 with a comparison group not necessarily drawn from another  
14 population, but from the same practices or same types of  
15 patients to see what their rates of infection are, another  
16 population with rheumatoid arthritis, you know, on  
17 comparable people. And then you'll get -- you know, you  
18 can use the same type of outcomes you used in the clinical  
19 trials that document or enumerate infections, characterize  
20 them by their severity and whether they require  
21 hospitalization or antibiotics, and then you'll get  
22 incidence rates over time and you'll be able to compare --  
23 and you can power that study based on rates that occurred  
24 in the trials pretty straightforward.

25 DR. PETRI: Several committee members asked for

1 further studies of B-cell function.

2 Dr. Jeff Siegel?

3 DR. JEFF SIEGEL: I wanted to just comment a  
4 little bit and ask a question about what David Felson was  
5 just saying. One concern is if you do a cohort trial, that  
6 you would want to enroll patients who were well matched and  
7 patients on Enbrel, and a concern is, would you have a  
8 concern that the patients who would be recruited who didn't  
9 take Enbrel might not actually be matched? How would you  
10 deal with that?

11 DR. FELSON: I'd deal with it two ways, Jeff.  
12 One thing I would do is try to ensure that we could get  
13 some baseline information on these subjects that allows you  
14 to characterize them with respect to the severity of their  
15 rheumatoid arthritis in ways that might predispose them to  
16 infection. So I think that's one way you then adjust for  
17 the analysis.

18 The other way, frankly, is, I was making an  
19 assumption that this would be fairly widely used, and that  
20 it wouldn't necessarily be used only among the most severe  
21 and most disabled patients. So I'm not sure I'm as  
22 concerned about it as you are.

23 DR. PETRI: Then, in addition, several  
24 committee members have brought up vaccination studies, and  
25 I think by that we mean antibody response after

1 pneumococcal vaccine.

2           Were there other studies? Dr. Harris?

3           DR. HARRIS: David, I'm really not sure how  
4 this would be done, but I think more than this rate, the  
5 other issue, although based on what we've seen so far  
6 perhaps one can't say that the response is any worse, I'm  
7 hoping -- I think that we need at least to see how in fact  
8 people with severe infections actually respond. Now, I'm  
9 not sure whether or not in fact the severity of the  
10 infections may be in fact enhanced in the presence of this  
11 agent. I'm not sure how that might be done. But I think  
12 that there's a theoretical risk certainly that it may be  
13 more severe.

14           DR. PETRI: But, Nigel, let me ask you as far  
15 as the next step, if someone has already had a severe  
16 infection, should they be allowed to continue on Enbrel?  
17 And we'll give the example of the poor lady who died of a  
18 staphylococcal sepsis. She had already had a wound  
19 infection after the arthroscopy, required a month of  
20 antibiotics. Should she go back on Enbrel if there's ever  
21 such a patient again?

22           DR. HARRIS: Actually, you raise a good  
23 question, and we decided that we wouldn't discuss that  
24 particular case, but it's interesting -- and I wasn't sure  
25 whether after arthroscopy and the initial infection, which

1 went for about 4 or 5 months -- I presume everything  
2 settled and became quiescent, and it then looked as if she  
3 had a second infection 8 months later that she was, one  
4 could argue, less able to respond to.

5 I think that there are certainly considerable  
6 problems with drawing from one case, but certainly I think  
7 given the theoretical possibilities here and you're not  
8 sure about accumulation and so on, as you said, I presume  
9 that one might (inaudible).

10 DR. PETRI: Dr. Yocum?

11 DR. YOCUM: I guess another issue, too, in this  
12 PI or whatever, what about patients who have other  
13 immunocompromise issues, such as diabetics, patients with  
14 evidence of hepatitis? How far do we go, I guess?

15 DR. PETRI: But the balance here is, a very  
16 effective drug will allow you to taper the prednisone. So  
17 you have to balance these immunocompromise issues, and  
18 remember, at least at this point, the immunocompetence data  
19 suggests that there might not be a problem. So, again, I'm  
20 afraid we're dealing with so many unknowns that I think  
21 that that's sort of the endpoint of the discussion.

22 But let me ask Dr. Karen Weiss, are there  
23 additional things in terms of infection that she'd like the  
24 committee to address?

25 (No audible response.)

1 DR. PETRI: So let's move on -- I'm sorry, Dr.  
2 Frieri, did you have a last word?

3 DR. FRIERI: One real quick question here. It  
4 would be very interesting to see if there is a steroid-  
5 sparing effect of this medication. Then that could be a  
6 Phase IV, to look to see if a steroid spares, lowering the  
7 amount of steroid. And we do know that in pressure ulcers,  
8 there is an increase of TGF-beta which can then change  
9 gamma interferon. Could the people with ulcers and wound  
10 infection have a disregulated TGF-beta causing less gamma  
11 interferon?

12 DR. PETRI: Dr. Weinblatt?

13 DR. WEINBLATT: I'd like to comment at least  
14 regarding the steroid-sparing aspects. As part of the  
15 long-term studies that we're involved in, clinicians do  
16 have the capabilities, even though it's not in a controlled  
17 fashion, to reduce background doses of methotrexate,  
18 corticosteroids, and non-steroidals as long as patients  
19 meet clinical response. This is not the same as a steroid  
20 withdrawal trial, and I'm sure, for those of you that are  
21 not aware, steroid withdrawal trials are exceptionally  
22 difficult to do and exceptionally difficult to maintain  
23 reproducibility and definition of response. This is more  
24 of a clinical experience in a patient who's receiving  
25 investigational drug, and then over time seeing whether one

1 can reduce background non-steroidal steroids and  
2 methotrexate in a semicontrolled fashion.

3 I think some of those issues regarding whether  
4 you could reduce NSAIDs, steroids, and methotrexate are  
5 being addressed now in the long-term studies.

6 DR. PETRI: Thank you.

7 Now moving on to Question 2 -- remember, I'm  
8 going to ask the audience to read the preamble themselves.  
9 I'll just read the part of the question that's in bold  
10 print. "Please discuss the risk of autoimmunity associated  
11 with Enbrel use. If approved, what information relating to  
12 the risk of new autoimmune disease should be included in  
13 the package insert? Should the sponsor be encouraged to  
14 conduct additional studies postmarketing to characterize  
15 the risk of developing positive autoantibody tests and new  
16 autoimmune disease with long-term treatment if Enbrel is  
17 approved? If so, please discuss the types of studies that  
18 should be considered."

19 And just to refresh our memory from this  
20 morning's presentations, there were no cases of new  
21 autoimmune disease, but to summarize the new autoantibodies  
22 that were found, comparing the 25-milligram dose with  
23 placebo, new ANAs in 12 percent versus 5 percent, new DNAs  
24 in 12 percent versus 4 percent, and with the more specific  
25 crithidia assay, new DNAs in 9 percent versus 0 percent.

1 And we saw the anticardiolipin data presented a few  
2 different ways, but because of assay problems, it was hard  
3 to get a definitive number.

4 Let me ask Dr. Harris if he'd like to start the  
5 discussion.

6 DR. HARRIS: Two comments to make. Of course,  
7 the first is that the presence of autoantibodies, as we  
8 well know, doesn't necessarily mean autoimmune disease, so  
9 certainly in terms of monitoring for autoimmune disease,  
10 for which I don't think there's enough data to say one way  
11 or another or whether indeed one in the very long term  
12 might not induce autoimmune disease autoantibodies, might  
13 not be the only way of measuring this.

14 But I wanted to comment about the  
15 anticardiolipin data, and just suffice it to say that it's  
16 common to get this sort of background noise with an agent  
17 such as this, and I think what should at least be  
18 encouraged perhaps in Phase IV is that in looking at the  
19 induction of the antibody levels, that in fact one try to  
20 get some sort of reliable method of quantitating the  
21 antibody, and certainly take note of patients with levels  
22 above 40 or 50 GPL or MPL units.

23 I think the background noise is one thing.  
24 That's to be anticipated. The critical question is, how  
25 many patients had relatively high levels for how long? And

1 I think that was not addressed here.

2 DR. PETRI: I had a few comments to make about  
3 this particular question. One is, I think we want to see  
4 long-term follow-up of those patients who made the anti-  
5 double-stranded DNA during the Phase II and Phase III  
6 trials. But I also wonder why we're only looking at lupus  
7 autoantibodies, because given our experience with  
8 penicillamine, should we be having a broader net, perhaps  
9 looking at anti-acetylcholine receptor myelocytic  
10 antibodies? And I welcome feedback from Immunex if perhaps  
11 you've already done this or whether you're considering  
12 doing this.

13 DR. HAYES: No, we have not.

14 DR. PETRI: Dr. Liang?

15 DR. LIANG: I thought, as an aside, you said  
16 that these were done in different labs. I'd actually ask  
17 the first question, and that is, what happens when you do  
18 them in one lab, in a good lab, like a Moe Reichland lab or  
19 something like that?

20 DR. HAYES: That was my misstatement. They  
21 were not done in different labs, but I was trying to show  
22 they were done with different kits and different lot  
23 numbers. We've only redone the pediatric data at a single  
24 time with a single kit and single lot number, and that's  
25 the --

1 DR. LIANG: Well, I guess first things first.  
2 I would just do it again, because I think that there's so  
3 much lab/lab, kit/kit variation that I'd hate for us to do  
4 a shotgun search for autoantibodies, because that would  
5 create all kinds of problems, not only for people thinking  
6 about starting it, but also for the clinician who has to  
7 deal with the written label recommendation to do that. It  
8 would be --

9 DR. PETRI: Matt, I wasn't suggesting this be  
10 part of the label, but this be part of a Phase IV study.

11 DR. LIANG: I wouldn't argue with any Phase IV  
12 study.

13 (Laughter.)

14 DR. PETRI: Dr. Hayes?

15 DR. HAYES: If it's okay, I would like Dr.  
16 Reichland to comment on our data. Dr. Reichland from  
17 Oklahoma City has reviewed all of the data for these  
18 autoantibodies.

19 DR. REICHLAND: First, let me say I did not  
20 advise Immunex on what to measure.

21 (Laughter.)

22 DR. REICHLAND: Because I think they measured  
23 far too many things.

24 I think Michelle has already said the most  
25 important bottom line, and that is that there were no new

1 cases of autoimmune disease of any type seen in this  
2 limited number of patients over this limited period of  
3 time.

4 But let me go to the issue that attracted my  
5 attention -- and I think would attract any rheumatologist's  
6 attention who looks at these data -- and that is the data  
7 about the anti-double-stranded DNA, because you probably  
8 all think, "Well, this is anti-double-stranded DNA. That's  
9 highly specific for lupus, and what's going on here?  
10 Shouldn't we be very concerned?" This test is highly  
11 sensitive. This is a radioimmunoassay. Three percent of  
12 normals -- 3 percent of normals -- are positive in this  
13 test. This is not the crithidia test. This is the  
14 radioimmunoassay. Five to 6 percent of rheumatoid  
15 arthritis patients are positive in this test at baseline.

16 What's going on here? What's going on here are  
17 at least two things. One is a highly sensitive test, and  
18 the second thing that's going on is that double-stranded  
19 DNA tends to unravel. It unravels in several ways. It  
20 unravels at the ends, unless it's circular, and this was  
21 not circular DNA that's in the kit, it's regular linear  
22 DNA, and if it's radiolabeled, the radiation breaks  
23 phosphodiester bonds, and if the technician doesn't have  
24 absolutely clean hands and had phosphodiester trace on his  
25 hands, you get more breaks and more single-stranded

1 regions.

2 Believe me, this DNA is not double-stranded.  
3 It is partly double-stranded, and it is partly single-  
4 stranded.

5 Normals have antibodies to single-stranded DNA.  
6 Rheumatoid arthritis patients, probably as many as 15 to 20  
7 percent of them in the assays that we use, which are also  
8 radioimmunoassays. Fifty-eight percent of the positive  
9 tests for anti-double-stranded DNA have negative ANAs. How  
10 can that happen? There are two ways that can happen. One  
11 is sensitivity. Radioimmunoassay is slightly -- probably a  
12 one log -- more sensitive than immunofluorescence. And the  
13 second way is that there are no single-stranded regions in  
14 the immunofluorescence substrate in the normal indirect  
15 immunofluorescence test. So you don't pick it up.

16 So a large part of what we're looking at is, to  
17 put it generously, noise. Noise.

18 Now, the crithidia is a different story. Of  
19 all of these positive tests, seven tests were positive for  
20 crithidia, so we need to look at that. First, let me say  
21 the only patient that consistently had a positive anti-DNA  
22 test by the crithidia was the lupus patient, who was known  
23 to have lupus, somehow got into this study, didn't get,  
24 seemingly, her old disease exacerbated by the Enbrel, and  
25 sailed through the study with her anti-DNA titer intact.

1 Of the other six, four had one positive and five negative  
2 tests.

3 Now, we don't even know about things like that,  
4 unless you run a lab the way I do and just do tests all the  
5 time, and when we see tests like that, we know they don't  
6 mean anything clinically. So forget the four. So we're  
7 down to two. We have two. In two instances, two of the  
8 five samples were positive, and they were intermittent.  
9 I'm not sure what that means. There's one patient to worry  
10 about. One patient had negative tests and then had two  
11 positive tests. I don't know what the follow-up is on that  
12 patient, but that patient should probably be followed.

13 So we have one test, one positive anti-double-  
14 stranded DNA out of 154 patients. I don't know, what is  
15 that, 0.6-something percent. What fraction of rheumatoid  
16 arthritis patients have a positive anti-double-stranded DNA  
17 by the crithidia test? There's a slide I want to show, two  
18 large series of rheumatoid arthritis patients at the  
19 beginning and at the end of a trial, one with Enbrel and  
20 one with Lenercept, and what I'm going to show you is that  
21 the positivity was the same at the end of the trial as at  
22 the beginning of the trial. Here on the left we have the  
23 Enbrel data. 0.6 percent were positive at the beginning,  
24 and 0.6 percent were positive at the end. This is a zero-  
25 sum game. We didn't gain anything.

1           If you look at most of the data, including the  
2 anticardiolipin data, and you look at the number that  
3 become positive and the number that go from positive to  
4 negative, you've got about nothing left when you finish.  
5 The same goes for ANA. It's a very sensitive test, as  
6 anybody who does these tests knows. We're talking about  
7 nanograms and fractions of nanograms, which turn into lots  
8 of picograms, of antibodies. It's nothing. And we have  
9 fluctuations around this little level here, and over time  
10 we have nothing.

11           So do I know whether this agent induces anti-  
12 DNA? I don't know. It doesn't look like it, from this  
13 study. Should we keep looking? Yes, I think we should  
14 keep looking. Should we require that this test be done  
15 over a period of years at a substantial cost? I think  
16 that's not so smart, although perhaps certain patients --

17           What should we do? We should do just the way  
18 we do with other patients. We should look at the patient.  
19 If something happens to the patient -- the platelet count  
20 goes down, a pleural effusion develops, a stroke -- then  
21 you evaluate the patient, and then you look to see what is  
22 this due to, and then you start doing these tests. But  
23 there is no data here that justifies the surveillance on a  
24 regular basis, the way it was done during the first 2 years  
25 of the study, for that to be continued into the future.

1                   So I think as part of Phase IV, certainly the  
2 patients will be followed closely. Whether they should  
3 have these tests done or not, we have no data to justify  
4 that.

5                   DR. HESS: I'll take you on.

6                   (Laughter.)

7                   DR. REICHLAND: Okay.

8                   DR. HESS: I think you're being just a little  
9 cavalier, which is fine. I've been fascinated this  
10 morning, all this sort of really paying such a lot of  
11 attention to the double-stranded DNA. As you know, for  
12 many years the "hallmark" or ticket to admission for drug-  
13 related lupus in fact was the positive antinuclear  
14 antibody, and there are a number -- nine of the patients, I  
15 think, had a positive antinuclear antibody.

16                   I'm entirely in agreement with your comments  
17 about the hodgepodge of the tests different ways, not  
18 stored sera, not done in the same lab. That really weakens  
19 this data, I think, and there might be an opportunity to  
20 really do it better.

21                   But I would point out to you, with all the  
22 other drugs, the procaindemyde hydralazine, more recently  
23 the minocycline, that in fact it was the ANA and not  
24 antibodies to double-stranded DNA which were the kind of  
25 pick-up, if you will. And so I would have a little concern

1 and would have thought that even in an intellectual way, it  
2 might be good to get some more information. I would point  
3 out that with the minocycline now we're finding antibodies  
4 to yankopanka coming up positive, and I would remind you  
5 all that with the penicillamine with rheumatoid arthritis,  
6 as you pointed out, Michelle, myasthenia gravis and various  
7 other autoantibodies appeared with time.

8           So I think it's an open question. I'm sure  
9 everyone in this room is aware of the English and European  
10 data with the monoclonals to TNF, and it's my  
11 understanding that there have been three to four patients  
12 with lupus recently described, and I think the trials have  
13 been put on hold. I'm not completely sure. So I think it  
14 is worthwhile continuing to pay some attention and maybe to  
15 do some other tests.

16           DR. REICHLAND: Can I say one thing?

17           DR. PETRI: Yes.

18           DR. REICHLAND: What would concern me is if a  
19 patient develops a positive test and then the titer goes up  
20 and it goes up higher and then it stays there, because  
21 that's what happens in all these drug-induced cases with  
22 pronestral and hydralazine, isoniazid, and so on -- that is,  
23 the antibody comes first, but it persists. It doesn't  
24 fluctuate. It's not near the baseline. Those are the  
25 kinds of observations that should be pursued. There aren't

1 too many of those, and --

2 DR. PETRI: Well, we're talking about such  
3 small numbers here. I mean, three out of 33 in the 25-  
4 milligram group got a new crithidia anti-double-stranded  
5 DNA.

6 DR. REICHLAND: Yes. Those were episodic,  
7 Michelle.

8 DR. PETRI: What if you look at another 100? I  
9 mean, I think that's my concern about small numbers.

10 DR. REICHLAND: I guess I didn't emphasize it.  
11 I run a clinical lab. We do these tests on everybody.  
12 This kind of thing is not unusual, to see a positive test  
13 at 1 to 10 or 1 to 30, and it goes away, and it doesn't  
14 mean anything.

15 DR. PETRI: Dr. Simon?

16 DR. SIMON: You know, everything we live, we  
17 live with risk/benefit. Everybody's brought up this issue  
18 about penicillamine, and we're confronting this issue of  
19 biologics as if they're a bugaboo because they're kind of a  
20 new way to think about drugs as we think about therapeutic  
21 interventions, and because they're so new, we get very  
22 nervous about them, and because they are biologics, perhaps  
23 they're modulating things that we don't understand, and  
24 they certainly haven't been studied in great detail.

25 I actually come down on Moe's side about the

1 idea that we should be studying these patients, they should  
2 be followed over time, but actually performing surveillance  
3 tests on them is not going to be as useful as being very  
4 careful and looking for drug-induced lupus clinically, as  
5 long as we have baseline data serologically attained when  
6 they begin the therapeutic intervention, and then if they  
7 in fact indeed develop real disease that we can measure and  
8 pick up and study, that indeed if their serologic tests are  
9 positive at that point in time or change compared to  
10 baseline, we'll learn more about that.

11 If this was a true drug, we may also not  
12 perceive that it's needed to surveillance the patients with  
13 tests that are not that good.

14 So I would urge us to consider a Phase IV trial  
15 that would include studying of the patients over time,  
16 getting serologic tests as a baseline on those patients,  
17 making sure the diagnoses are correctly made, and then  
18 follow the patients clinically.

19 DR. PETRI: So you're echoing my suggestion  
20 that this be done as Phase IV, but not be part of the  
21 labeling?

22 DR. SIMON: Oh, definitely not be part of the  
23 labeling.

24 DR. PETRI: Dr. Hayes wanted to respond, and  
25 then Dr. Frieri.

1 DR. HAYES: I just wanted to reassure the  
2 committee that in our long-term trial, 16.0018, we are not  
3 planning on doing serial studies, but we do have specific  
4 CRFs, so every patient's data concerning any evidence of  
5 autoimmune disease is being collected in that trial, and,  
6 obviously, if there was any positivity, they would be  
7 tested, and those are patients out of our current trials,  
8 where we have data on them for these assays at this point  
9 in time.

10 DR. PETRI: Dr. Simon has another comment.

11 DR. SIMON: I had the opportunity to sit on  
12 another advisory committee as it concerned and considered a  
13 monoclonal antibody to TNF-alpha, and I was struck by the  
14 biologic responses in that subset of patients, although  
15 profoundly smaller in number, that were studied. Even if  
16 we think this is a small number in certain ways, those  
17 numbers were even smaller. And it's interesting from a  
18 biologic point of view what those responses were compared  
19 to what we're seeing here, and I think that's fascinating.  
20 I can't explain it. I have no idea why a monoclonal  
21 antibody to TNF-alpha would do what it did versus what a  
22 soluble receptor to TNF-alpha with a humanized Fc portion  
23 on it would not do the same kinds of things.

24 I think it's very interesting, but there's no  
25 reason we should suspect there will be exactly the same

1 kind of responses just because they're biologic agents. On  
2 the other hand, it's fascinating that there were any  
3 changes, because in the context of the monoclonal antibody,  
4 there were actually antibody responses to the monoclonal  
5 antibody. In this case, there were not, so perhaps this is  
6 truly modulating in a very, very small number of patients  
7 some immune function that it will be interesting to study  
8 over time.

9 DR. PETRI: Dr. Frieri?

10 DR. FRIERI: Yes, I agree with Dr. Reichland's  
11 comments. I also run a clinical lab and see patients, and  
12 I think one needs to individualize and not do massive  
13 screening just to look for these antibodies. However, in  
14 subsets of patients, it should be up to the treating  
15 clinician, if they suspect someone has, like, a thyroid  
16 disease and needs to look at thyroid, clinically to follow  
17 patients, and then to measure the antibodies.

18 DR. PETRI: Dr. Hayes, did you have another  
19 comment?

20 DR. HAYES: I was just going to say that I  
21 would like to echo what Dr. Simon's saying, that even  
22 though we may inhibit TNF, as the monoclonal does, that  
23 these agents are not the same. They have some significant  
24 differences in terms of the way they're dosed, their half-  
25 life, the length of time they're present in the body, their

1 immunogenicity. There are tremendous differences between  
2 the soluble receptors and monoclonal antibodies, and I  
3 guess I would make a plea that all anti-TNF therapies are  
4 not the same and shouldn't necessarily be treated the same.

5 DR. JAY SIEGEL: On that note, I would note,  
6 though, there's also a difference in the patient  
7 population. There were two clinical cases that looked like  
8 autoimmune disease, and one of them was development of  
9 arthritis, which in Crohn's disease is more likely to be  
10 picked up as a sign of a lupus-like syndrome than it is in  
11 a patient with rheumatoid arthritis. So in some sense  
12 there's less sensitivity in this population as well.

13 DR. PETRI: To summarize where we are, I don't  
14 think I heard anyone state that they wanted this to be part  
15 of the labeling in the absence of a single case of  
16 autoimmune disease, but I heard several comments from the  
17 committee in favor of a Phase IV study with high-quality  
18 assays at baseline and then follow-up, and I think most of  
19 us would want, Dr. Hayes, not just clinical follow-up, but  
20 some serial studies in those patients as well, especially  
21 for some of the things that weren't quite so clear, such as  
22 the anticardiolipin data because of the kit problems that  
23 were faced.

24 Dr. Weiss?

25 DR. WEISS: Just for clarification, you

1 mentioned a number of times getting some baseline so that  
2 you'll have that to go back to should a patient develop  
3 some type of new autoimmune disorder. Is there, then, a  
4 panel basically of various baseline autoantibodies? I  
5 mean, everybody's been focusing on lupus, but you mentioned  
6 no concern with myasthenia gravis and with other agents and  
7 autoimmune thyroid disease. For the ability to be able to  
8 go back and look at that serum at baseline, should there be  
9 basically a set type of anti-whatever antibodies that are  
10 evaluated at baseline in patients?

11 DR. PETRI: One advantage of storing sera is,  
12 you can always go back and add, but let me ask Dr. Hess  
13 what would she pick as the minimal panel.

14 DR. HESS: I mean, if now you're talking money,  
15 that's not fair. Presuming endless funds, an ANA with a  
16 titer, an accepted antibody to double-stranded DNA if the  
17 ANA is positive, and I think perhaps an antithyroid  
18 antibody screen, and I'm not sure about doing things like  
19 anti-SM, anti-ORMP. We haven't gone into any discussion of  
20 that, and there's actually very little information.

21 DR. PETRI: But you would add anticardiolipin.

22 DR. HESS: And anticardiolipin with antibody,  
23 yes, of course.

24 DR. PETRI: What about anti-acetylcholine  
25 receptor? I mean, should we go on the basis of our

1 penicillamine experience?

2 DR. HESS: No, I think I would watch for the  
3 symptoms.

4 And in terms of the description of what  
5 physicians should follow, I know -- and I would entirely  
6 agree -- that you're not going to recommend doing screening  
7 ANAs, et cetera. But I think perhaps a sentence should say  
8 that we really do not know the natural evolution of whether  
9 or not autoantibodies or autoimmune disease will appear,  
10 and the physicians should be cautioned to watch out for  
11 these very carefully, something along those lines.

12 DR. PETRI: Dr. White?

13 DR. WHITE: Michelle, I'd like to voice a  
14 minority opinion to what you said. I think you said that  
15 you thought the Phase IV study should include routine  
16 surveillance of a panel of autoantibodies in the absence of  
17 any particular clinical symptoms with this, that the panel  
18 of autoantibodies ought to be done routinely. My minority  
19 view is that I see no need for this in the absence of  
20 clinical symptoms.

21 DR. PETRI: But our problem, Barbara, though,  
22 is then we'd never get any data, because you're not going  
23 to get that data from the use in the general population.

24 DR. WHITE: We spend a lot of time educating  
25 our peers about when to order ANAs.

1 DR. PETRI: Dr. Brandt had a comment.

2 DR. BRANDT: It's the same issue of  
3 clarification.

4 DR. PETRI: Into the microphone, please.

5 DR. BRANDT: It comes to this issue of  
6 clarification. I had thought that what you were suggesting  
7 was a Phase IV study, a clinical trial on a group of  
8 defined patients with baseline serologies or the panel such  
9 as the one that Evelyn mentioned, who would then be looked  
10 at prospectively, who might have no suggestion of new  
11 autoimmune disease --

12 DR. PETRI: Correct. Dr. Simon and I, I think,  
13 both voiced a wish for such a Phase IV study.

14 DR. BRANDT: Yes, which is quite different from  
15 recommending that to clinicians as a baseline panel to be  
16 done on everybody --

17 DR. PETRI: No one on the panel has recommended  
18 this to clinicians, but Dr. White objected to doing the  
19 Phase IV study.

20 DR. WHITE: I objected to doing at times X, Y,  
21 and Z a predefined panel of autoantibodies in the absence  
22 of clinical symptoms.

23 DR. BRANDT: In clinical practice.

24 DR. WHITE: No, no, in the studies.

25 DR. BRANDT: Okay.

1 DR. PETRI: Other comments? Let me ask Dr.  
2 Weiss, Dr. Siegel, if they have other concerns they'd like  
3 us to address about the autoimmunity issue.

4 DR. JAY SIEGEL: Just one clarification.  
5 Cannot most or all of the relevant serological studies, if  
6 a Phase IV study is to be done, be done on frozen, bank-  
7 stored sera --

8 DR. PETRI: Yes.

9 DR. JAY SIEGEL: And are they not in fact  
10 better done in parallel with baseline?

11 PARTICIPANT: Yes.

12 DR. JAY SIEGEL: And if they're only to be done  
13 in patients in whom symptoms develop, then is not the best  
14 thing to do to get the baseline sera and then do the right  
15 tests for the symptoms that develop when the symptoms  
16 develop? I mean, am I missing something?

17 DR. PETRI: There are several different ways to  
18 design such a Phase IV study. The cheapest is to do the  
19 baseline serologies and follow the patients clinically.

20 DR. LIANG: Well, actually, can I just add to  
21 that?

22 DR. PETRI: Dr. Liang?

23 DR. LIANG: I think it would be better  
24 methodology that you'd draw the blood and store it, and  
25 then that you would do a systematic system review or

1 something like that as part of the protocol, and then when  
2 something happens, you'd sort of do an incidence case-  
3 control design, and then yank blood and do the appropriate  
4 studies. Because I think once the cat is out of the bag,  
5 so to speak, that you know what the person's profile is at  
6 baseline, it might actually increase the detection rates in  
7 a serious way.

8 So I think it could be done more cheaply just  
9 by taking a good history, but making it systematic and  
10 storing the blood.

11 DR. PETRI: Dr. Simon, did you have an  
12 additional comment?

13 (No response.)

14 DR. PETRI: So I think there is general  
15 agreement about doing the Phase IV study. There was  
16 disagreement about whether there should be serial  
17 serologies or just following the patients clinically.

18 The third question is one that will require  
19 panel votes. Dr. Silverman is a non-voting member. He can  
20 participate, of course, in all the discussions, but not  
21 vote. And I'm not going to read the preamble. I'm just  
22 going to read the questions that are in bold. I'm going to  
23 take them one at a time.

24 "Do the safety and efficacy data support an  
25 indication for use of Enbrel as monotherapy in patients

1 with active RA (please define) who have failed DMARDs and  
2 have disease severity similar to patients studied?" As we  
3 discuss this, not only will we have to define active RA,  
4 but I think we're going to have to define which DMARDs.

5 Dr. Simon, did you want to start?

6 DR. SIMON: I was just actually scratching my  
7 cheek, but on the other hand --

8 (Laughter.)

9 DR. SIMON: I'll remember not to do that the  
10 next time.

11 This is a very difficult question, obviously.  
12 That's why it's the longest question on the choices. I  
13 actually would come down on favoring not approving this  
14 drug to be used in anybody who has rheumatoid arthritis at  
15 this stage of the game, based on the dearth of information  
16 we have on all the things we've discussed so far over the  
17 last 6 hours or so. I think that it should be made  
18 available. I think the drug is a useful drug. I don't  
19 entirely understand its risks, and, therefore, I tend to  
20 fall on the side of using it in people that have no  
21 alternatives or who have failed other drugs or who are  
22 quite rapidly worsening as opposed to using it as a single  
23 drug in the patient newly diagnosed with rheumatoid  
24 arthritis.

25 Furthermore, until we have more data about the

1 altering of the natural history of the disease, as either  
2 defined by X-ray data or in the context of actually useful  
3 functional outcome data, which I do not believe has been  
4 presented us today, I think that there are drugs that have  
5 been approved by the FDA that actually have demonstrated a  
6 structural change and functional change, and, therefore, I  
7 am not entirely sure this drug should be used first in the  
8 context of those drugs that are now available.

9 So, therefore, in conclusion, I would opt for  
10 these drugs not to be used early, not to be used in  
11 patients who have not been given the opportunity to be on  
12 other drugs, and I'd be happy to define what those other  
13 drugs are, and maybe it's okay to use them in combination  
14 with at least methotrexate, because we have data about  
15 that.

16 DR. PETRI: Again, let me press you to define  
17 that list of failed DMARDs. Does it include hydroxy  
18 chloroquine?

19 DR. SIMON: I think that because we now have  
20 the data on methotrexate altering structure and function,  
21 lefludamide altering structure and function, that until we  
22 have equivalent data from this soluble receptor to TNF-  
23 alpha, I don't think it's appropriate to use it before  
24 those two drugs. I don't have the same data about gold, at  
25 least of the same quality. I also don't have that same

1 data about hydroxy chloroquine or sulfasalazine, and I  
2 don't have it about combination therapy with sulfasalazine  
3 and hydroxy chloroquine. I only have it with those two  
4 drugs, and I would lean toward the evidence base that's the  
5 paradigm of today, and I would go with the data that we  
6 have.

7 DR. PETRI: Okay. So right now what we have on  
8 the table is a definition of failed DMARDs as methotrexate  
9 and lefludamide.

10 Dr. White?

11 DR. WHITE: I need clarification, Michelle.  
12 I'm not sure what we're discussing. I heard a lot of  
13 things put together. We can discuss whether or not we  
14 think it's effective for signs and symptoms, whether or not  
15 we think it's effective for structure, which we weren't  
16 even asked to, so I don't know why that should come into  
17 the discussion about this part of it, and my view of the  
18 data that we were presented is, I am convinced that the  
19 risk/benefit ratio that we were presented, limited as we  
20 all recognize, suggests that in fact it is a beneficial  
21 drug for signs and symptoms in people who have failed  
22 DMARDs, who have active RA as it was defined.

23 DR. PETRI: But the question is asking us, can  
24 a patient use this drug who has not failed DMARDs?

25 DR. WHITE: If that's the question, then I

1 would say we don't have evidence for that.

2 DR. PETRI: Dr. Abramson?

3 DR. ABRAMSON: I tend to agree in many ways  
4 with what Barbara was saying, that the data that we have --

5 PARTICIPANT: Steve, could you speak up?

6 DR. ABRAMSON: Yes, I'm sorry. I mean, I think  
7 the drug for signs and symptoms is very clearly quite  
8 effective. We don't have sufficient data on safety. But  
9 clearly the patient profiles that were entered into these  
10 studies I think would meet the kind of patients that I  
11 would use this for, meaning I would not use it as first-  
12 line therapy. I'm not sure I would make them have to fail  
13 any two specific DMARDs, but this is a very messy area.

14 But I think the same kinds of criteria that  
15 were used make sense. I think because it's a biological,  
16 we shouldn't apply different kinds of criteria for it, and  
17 that means a lot of things, and it also means that other  
18 drugs may bring 1,000 or 3,000 patients to this committee  
19 with several years of experience, and we get more safety  
20 data. Here we have 500 patients treated for 6 months,  
21 which I think is clearly much less than we're used to  
22 seeing and really doesn't allow us to make long-term  
23 statements about safety, and that is of considerable  
24 concern.

25 And I think as a final comment, so I don't

1 forget, the patient-years issue can really give us no  
2 comfort with regard to cancer and particularly where  
3 there's a latent period in these drugs, where in cytotoxic  
4 drugs we may see 3 or 5 years' delay before these cancers  
5 appear. So I would say that we cannot make any statement,  
6 not put that in any way in the package insert as useful  
7 data.

8 DR. PETRI: Dr. Silverman?

9 DR. SILVERMAN: I just want to ask a  
10 clarification, because it will get on to the pediatric  
11 rule. If the indication is slightly different, like, I  
12 would recommend in pediatrics slightly different than I am  
13 hearing about in adult RA, is that legitimate?  
14 Specifically, I think there may be an indication in  
15 pediatrics prior to failure of other DMARDs, especially in  
16 view of the fact that very few DMARDs, with the exception  
17 of a single DMARD, have been proven to be effective. So  
18 it's really clarification.

19 DR. PETRI: We're going to be discussing the  
20 pediatric situation as one of the questions, so I'm going  
21 to ask you just to postpone that discussion.

22 Dr. Tilley?

23 DR. TILLEY: Michelle, I've lost -- which  
24 question are we on?

25 DR. PETRI: We're on Question 3a. We have to

1 do these one at a time.

2 DR. JAY SIEGEL: Actually, we're discussing the  
3 whole set of Question 3, which I think is excellent. Just  
4 for those who haven't read them through or to whom our  
5 language may not be clear, let me explain the question  
6 structure or at least the intended question structure.

7 A is specifically about perhaps the narrowest  
8 indication we're discussing and involves both use alone and  
9 in prior failures with relatively advanced disease, without  
10 carefully defining exactly what those terms mean, and then  
11 B discusses or asks whether it should be expanded as  
12 proposed to a broader indication which does not take into  
13 account either disease severity or prior DMARD use.  
14 Conceivably those two questions could be answered  
15 differently. C has to do with use in combination with  
16 methotrexate, addressed by a separate study, the  
17 combination with other DMARDs, and then a question about  
18 rheumatoid factor.

19 But having said that, I think the discussion  
20 that's going on is very helpful to us, and I don't want to  
21 limit it necessarily to discussing A prior to B or  
22 whatever. It's hard to discuss one without the other. But  
23 when you get to voting, that's what we're looking for,  
24 first kind of, is there any indication or should there be  
25 one for, say, refractory severe patients? Should it be

1 broader than that, and should it include combinations?

2 That's the advice we need.

3 DR. PETRI: Dr. Tilley?

4 DR. TILLEY: Because I thought I heard a  
5 consensus about A.

6 DR. PETRI: We will vote, yes.

7 DR. TILLEY: So that was where I was getting  
8 confused.

9 DR. PETRI: All right. Dr. Katona, then Dr.  
10 Harris.

11 DR. KATONA: There is one question in my mind  
12 that I don't think we have discussed here today. If we  
13 started a patient on Enbrel and she responded to the  
14 therapy, how long are we going to continue this? Is this  
15 going to be a drug that is going to solve all of our  
16 problems? The data that we looked at is 20 percent  
17 improvement. So in my mind, we probably ought to look at  
18 it that this is going to be one additional drug in our  
19 armamentarium, and the more flexibility given to the  
20 rheumatologists, the better off we are.

21 I could imagine a scenario of somebody being  
22 really sick, having a flare, starting her on Enbrel, and  
23 eventually being able to get her off and just have her on  
24 methotrexate or whatever. So I think I would be very much  
25 opposed to just very quickly define, since we really don't

1 have a good clinical experience so far.

2 DR. PETRI: Okay. Now I'd like to actually  
3 take a vote on A, because if we can vote on A, where there  
4 may be some consensus, we'll then move on and further  
5 discuss some of the others.

6 I'm sorry, Dr. Moreland has a comment.

7 DR. MORELAND: I'd just like to make a couple  
8 of comments. I think we're missing the point here when  
9 we're talking about failing a DMARD. Failing a DMARD is  
10 important for a clinical trial to have a homogeneous  
11 patient population, and used as one of our criteria to have  
12 a patient population that has active disease, but I doubt  
13 that we could reach consensus in this group today as to  
14 what a failure of hydroxy chloroquine is or a failure of  
15 methotrexate is. So I think that's a real critical issue,  
16 just to say that we're going to require that.

17 And more importantly, 30 to 40 percent of the  
18 patients I take care of don't take methotrexate or can't  
19 respond to it, and they may not be willing to take other  
20 drugs, if you approve lefludamide or others, because of the  
21 potential side effects. So I think we need to give a lot  
22 of thought to putting us into a box. I think this is a  
23 patient/doctor decision based on available data.

24 DR. PETRI: Larry, I want to make sure -- I  
25 don't think that agreement with Part A means that people

1 can't agree with the other questions as well. So this was  
2 just a starting point.

3 Dr. Simon?

4 DR. SIMON: I would actually make a comment for  
5 clarification of my rambling statement that I think, Larry,  
6 I wasn't suggesting that that wasn't included in the idea  
7 of failing a DMARD. If a patient decides they can't take a  
8 drug which a physician suggests based on certain criteria,  
9 and then they are left with the choice of this particular  
10 drug as the intervention, I don't think that that's wrong,  
11 and I don't think a label would keep them from doing that.  
12 I think that the issue, though, is, until we have further  
13 data both from a safety point of view, which I entirely  
14 agree with, as well as an efficacy point of view, I don't  
15 think we have the data that would suggest that this should  
16 be the choice first. And that's just my point.

17 DR. JAY SIEGEL: In fact, a failure or lack of  
18 ability to tolerate --

19 DR. SIMON: I can't hear you.

20 DR. JAY SIEGEL: Failure or lack of ability to  
21 tolerate other therapy is used not only in clinical trials  
22 to ensure homogeneity, but not uncommonly in labeling of  
23 new products, for reasons such as you just cited.  
24 Particularly in the oncology experience, it is not uncommon  
25 for an agent to come on the market originally for use as

1 salvage therapy, if you will, in people who have failed or  
2 cannot tolerate standard therapy, often because either its  
3 utility in first-line use is unknown, its relative utility  
4 compared to alternatives is unknown or suspect, or little  
5 enough is known about its safety profile or enough is  
6 unknown about it to make it unwarranted at the time of  
7 licensure to consider it as a first-line agent when other  
8 better-known agents are available.

9 So not to suggest that that is necessarily the  
10 answer here, but simply to say that that does appear in  
11 labeling not uncommonly for products, depending on what the  
12 data show.

13 DR. PETRI: Dr. Abramson?

14 DR. ABRAMSON: I would like to just pick up on  
15 that to explain why I agree with what Dr. Simon had said,  
16 and that is why there should be other DMARDs, and that is  
17 the sense that I think many of us have that there is not  
18 yet enough data to give this drug the same imprimatur that  
19 we've given methotrexate and other drugs. There's enough  
20 data to get enthusiastic that it is a terrific drug for  
21 many people, but I think the piece that we haven't  
22 discussed is more safety data, whether it's in, say, Phase  
23 IV, to get beyond 500 at 6 months and 190 at 1 year. I  
24 don't think that's the kind of numbers that we normally  
25 like to approve a drug just to go out there and be

1 competitive in the marketplace, because we don't have that  
2 2- and 3-year follow-up.

3 I think when that comes in and if it bears out  
4 that it is as safe as these other drugs, then I think those  
5 other issues, whether it's a first-line drug or not, would  
6 be different. But right now I think some of us have great  
7 hesitancy to give it the same endorsement based on the  
8 numbers of patients and the length of time.

9 DR. PETRI: Dr. White, then Dr. Paulus.

10 DR. WHITE: I agree with you completely, Steve,  
11 and I would like to make the additional comment that the  
12 data should be forthcoming from the company about use of it  
13 as a first-line agent. So that I don't think -- while I  
14 agree we shouldn't box ourselves into positions, we  
15 shouldn't be so broad when we don't have data and they will  
16 be coming.

17 DR. PETRI: Dr. Paulus?

18 DR. PAULUS: I think we're discussing our  
19 anxieties about the future because we don't know what the  
20 future holds. If we look at the information that we have,  
21 which is fairly substantial, this drug is very effective,  
22 and it's very safe. We really don't see much in the way of  
23 side effects in the patient population which we've been  
24 presented with. And if we looked at a similar group of  
25 patients with methotrexate or with penicillamine or with

1 prednisone, we would be able to detect indications if there  
2 were problems. Now, that doesn't mean there won't be any  
3 with this, and what we need is more experience to feel more  
4 comfortable with it, and we'll get that experience probably  
5 after it's marketed.

6 In terms of using it in early patients, there's  
7 a large study under way in patients where it's used de  
8 novo, who have never had methotrexate, comparing it with  
9 methotrexate. We had a lot of information from that about  
10 its safety, its effectiveness vis-a-vis methotrexate, and  
11 also structural damage over a several-year period, so I  
12 think that we want to be sure that we're not just  
13 perseverating about our anxieties too much here.

14 DR. PETRI: I think the point is that with the  
15 lack of radiographic data, it's hard to know where this  
16 fits in at this point.

17 I'm going to insist that we vote on Part A,  
18 because we're sort of discussing so many in a row here. So  
19 A is, can this drug be used as monotherapy in patients with  
20 active RA who have failed DMARDs and have disease severity  
21 similar to patients studied?

22 We'll go around and ask for yeses and nos. Dr.  
23 Katona, you're first.

24 DR. KATONA: Yes.

25 DR. PETRI: Dr. Goldsby?

1 DR. GOLDSBY: Yes.

2 DR. PETRI: Ms. Malone?

3 MS. MALONE: Yes.

4 DR. PETRI: Dr. Harris?

5 DR. HARRIS: I really can't vote for A without  
6 voting for B.

7 DR. PETRI: We'll vote for B next.

8 DR. HARRIS: So I'll go for a no, so that I'll  
9 vote for B as a yes.

10 DR. PETRI: Well, no, but these are not  
11 exclusive. You can vote yes for both.

12 DR. HARRIS: Okay.

13 DR. PETRI: So do you want to change your vote?

14 DR. HARRIS: Okay. It's how it's worded, B,  
15 but I'll vote yes.

16 DR. PETRI: Dr. Frieri?

17 DR. FRIERI: Yes.

18 DR. PETRI: Dr. Yocum?

19 DR. YOCUM: Yes.

20 DR. PETRI: Dr. Simon?

21 DR. SIMON: Yes.

22 DR. PETRI: Dr. Luthra?

23 DR. LUTHRA: Yes.

24 DR. PETRI: Dr. Liang?

25 DR. LIANG: Yes.

1 DR. PETRI: Dr. Tilley?

2 DR. TILLEY: Yes.

3 DR. PETRI: I vote yes.

4 Dr. Abramson?

5 DR. ABRAMSON: Yes.

6 DR. PETRI: Dr. Callahan?

7 DR. CALLAHAN: Yes.

8 DR. PETRI: Dr. Hess?

9 DR. HESS: Yes.

10 DR. PETRI: Dr. White?

11 DR. WHITE: Yes.

12 DR. PETRI: Dr. Pucino?

13 DR. PUCINO: Yes.

14 DR. PETRI: Dr. Felson?

15 DR. FELSON: Yes.

16 DR. PETRI: Okay. So it's unanimous.

17 Now, I think B is a little more controversial,  
18 and in fact that's what we've mainly been discussing is B.  
19 Is there additional discussion before we vote on B?

20 Dr. Harris?

21 DR. HARRIS: I just want to echo again, I  
22 guess, what Dr. Paulus is getting to. DMARDs are not  
23 innocuous therapy. These agents, such as methotrexate,  
24 gold, penicillamine, are all agents associated with quite  
25 severe side effects. This new agent, Enbrel, is, based on

1 the data we have, efficacious. The side effects so far are  
2 pretty minimal when you compare it with some of the other  
3 agents that we have.

4 I understand the nervousness, and I'm equally  
5 nervous about something as new as this, with as limited  
6 data as we have, but in terms of where we're going with  
7 this, I think one does need to bear in mind that DMARDs are  
8 quite -- they have quite more side effects than Enbrel.

9 DR. PETRI: Dr. Simon, then Dr. Weinblatt.

10 DR. SIMON: Nigel, I think you're absolutely  
11 correct, but we have to remember that at least with the  
12 known DMARDs, at least two of the known DMARDs that are  
13 presently on the market, we know something about their  
14 effect on structure and function, which prior to last year,  
15 although some investigators knew, the world did not know.  
16 It may not be perfect, and the structure/function data may  
17 not be as much as we'd like, but at least we have it, and  
18 it suggests that these two drugs do decrease progression of  
19 disease and improve function and decrease disability, and  
20 that's good data.

21 It is possible this drug will do the same.  
22 Absolutely. And Dr. Paulus is absolutely correct that in  
23 fact someday we'll have that data, and perhaps it will be  
24 very soon. Unfortunately, we don't have it now, and the  
25 disability data and functional data is not enough to be

1 actually applied, and, therefore, from a risk/benefit  
2 analysis, for me, it seems that although this drug is very  
3 good for signs and symptoms, I would prefer to have and  
4 start with a drug -- I think it's more appropriate to start  
5 with a drug, although perhaps riskier from a safety point  
6 of view in certain ways, one that has shown benefits signs  
7 and symptoms, structure and function, and has been proven  
8 and indicated for that.

9 That's the only reason I bring this up. This  
10 may be exactly the same, and it may be a great drug for  
11 signs and symptoms, but at least until the data exist  
12 otherwise, I still would resist using it as first-line  
13 therapy in these patients as described in B.

14 DR. PETRI: Dr. Weinblatt?

15 DR. WEINBLATT: I'd just like to make one  
16 comment, irrespective of my position as an investigator and  
17 a consultant to Immunex. I'd like to remind the panel that  
18 the labeling is going to be extremely important for our  
19 colleagues in practice. If you have very rigid labeling,  
20 it will affect the ability of a rheumatologist to make an  
21 individualized decision regarding a specific patient, not  
22 just with regard to medico-legal implications, for which  
23 there are many now when you use an off-label use, but also  
24 reimbursement of a compound for our patient population.

25 I think you should have confidence in the

1 rheumatology community to look at the data with specific  
2 drugs in which there are questions regarding lack of safety  
3 data, there are issues regarding toxicity, there are issues  
4 regarding other aspects, and let the rheumatologists make  
5 the decision where they're going to use the drug in  
6 clinical practice. I am concerned if there's a very rigid  
7 label, that it could take many years for that label to  
8 change, in which case the rheumatology community are going  
9 to be placed at risk, and potentially our patients.

10 I think this is really a question --

11 DR. PETRI: Mike, I don't think you're  
12 addressing the panel's concern, which is, we don't have  
13 radiographic data.

14 DR. WEINBLATT: I understand that, but in 1988  
15 when methotrexate was approved, there was no radiographic  
16 data, either, and we don't necessarily make the decisions  
17 about clinical practice based upon an X-ray.

18 DR. PETRI: Yes, but I think standards have  
19 increased since 1988.

20 Dr. Felson?

21 DR. FELSON: I must take issue with both Larry  
22 Moreland and Mike Weinblatt. I think the advice is not  
23 helpful here. I think there's not enough safety data here  
24 to feel comfortable on our part if we feel that we want to  
25 protect patients who might experience an adverse event that

1 we currently can't anticipate very well. There's just not  
2 enough data, and I think that's, for me -- and I'll echo a  
3 lot of what Steve said and a lot of what Barbara said --  
4 that's the overriding issue here.

5           When the other drugs you're talking about were  
6 approved, there was considerable safety data, some of it  
7 not necessarily that reassuring, because many of those  
8 drugs had been used for other purposes, so we knew what to  
9 expect. And we know a lot of what to expect -- it's the  
10 devil we know. Okay, yes, they're not terribly safe, but  
11 at least it's the devil we know. Here we don't know what  
12 this is going to do over long periods of time. I don't  
13 necessarily want patients to feel comfortable -- doctors to  
14 feel comfortable prescribing to patients this as a first-  
15 line treatment before they've received anything else  
16 without -- I mean, there are many examples, vanoxiprofen  
17 and others, of situations where that occurred and we felt  
18 bad for it later.

19           I think this needs to be reserved initially for  
20 people who have taken other things, and then they can get  
21 this after they've tried other things, where the devil we  
22 know, as it were, and not the devil we don't know.

23           DR. PETRI: Dr. Katona, then Dr. White.

24           DR. KATONA: I would like to suggest that we  
25 break into two different sections this question which is

1 posed to us. When we're looking at disease severity, a  
2 patient who has mild disease, I think I would have a really  
3 hard time letting any rheumatologist pick up an agent which  
4 does not have enough safety data. So I might like to vote  
5 differently on the first part of the question. Then, prior  
6 DMARD use, I think I agree on that with Dr. Weinblatt that  
7 we have to give the judgment to the individual  
8 rheumatologist. So please consider my recommendation.

9 DR. WHITE: I would disagree with Dr.  
10 Weinblatt's statement. We do have to allow a degree of  
11 flexibility, but the reason we are all here today is to  
12 help look over the data, judge them based on what is  
13 presented, and help provide guidance by the labeling to the  
14 practicing physician rather than say the practicing  
15 physician, independent of what we say and the data that are  
16 presented, will know how to do this.

17 And that, Mike, is the leap of faith you ask us  
18 to take that I'm not willing to do. We do not have data.  
19 I could not judge something in the absence of any data.

20 DR. PETRI: Dr. Moreland?

21 DR. MORELAND: I just want to make a comment.  
22 I think a lot of the discussion has been generating around  
23 X-ray changes. We haven't come forth today with  
24 radiographic data and asked for indication, we've asked for  
25 signs and symptoms. So I think you're setting a different

1 bar for what the real purpose of today's meeting is, and  
2 it's not around radiographic changes, it's about treating  
3 signs and symptoms and deciding what level of disease  
4 activity patients must have and what other hoops they must  
5 jump over to get in to receive such drugs.

6 I would echo, again, Mike's comment and Hal's  
7 comment. We need to, I think, in my view, let the  
8 practicing rheumatologists make decisions based on the  
9 data, and I don't think we should underestimate their  
10 ability to do that.

11 DR. PETRI: Dr. Simon?

12 DR. SIMON: Larry, you're arguing in a  
13 regulatory point of view, and I'm arguing from the point of  
14 view that there's more than regulatory information when you  
15 talk about the indication for structure and function, and  
16 I'm not separating out the two. There are data about  
17 function as well that's lacking here. In fact, regardless  
18 of the regulatory environment of indication, there are some  
19 drugs that have been demonstrated to change those other  
20 issues, and that's probably more important than signs and  
21 symptoms, although I recognize that patients want to feel  
22 better. But fundamentally disability is tied not to just  
23 how you feel, but structure and function, so that's why I'm  
24 arguing that.

25 DR. PETRI: Dr. Abramson?

1 DR. ABRAMSON: Since we've entered into this  
2 discussion, you have to understand, there are only 192  
3 people that have been presented to us that have been on  
4 this drug for a year. If the cancer occurs in 100,000  
5 people, we just can't be sure -- I don't think a drug has  
6 come to this panel in the last 3 years I've been on it with  
7 so few patients being studied, and yet be a drug that we  
8 know is a modulator of the immune system.

9 So the issue is, it's really terrific that we  
10 were impressed enough with its signs and symptoms to say  
11 this is a good drug to release, but that is a big step,  
12 given 192 people. I think if any other -- you know, if a  
13 guy came through with magnets with 190 people, we'd kick  
14 him out of the room.

15 (Laughter.)

16 DR. ABRAMSON: But I think all we're saying is  
17 that until we get more data in studies that are obviously  
18 ongoing and maybe that data will come out, that 192 will be  
19 2,000 or whatever it is, and there will be some comfort.

20 DR. JAY SIEGEL: With regard to amount of data,  
21 I feel like perhaps I should point out -- because it has  
22 been pointed out that narrow indications sometimes can  
23 impair ability to try different utilizations, or  
24 reimbursement issues. I'd also like it to be borne in mind  
25 that broad indications sometimes impair the ability to do

1 clinical studies, particularly to do controlled clinical  
2 studies, which for some questions are the only way and for  
3 most questions one of the best ways to get answers.

4 DR. PETRI: Okay. I think it's probably time  
5 to come to a vote, but I first have to get a committee  
6 consensus about whether we vote on B as written or whether  
7 others agree with Dr. Katona's suggestion that we split it  
8 in half. Does anyone want to split this in half, other  
9 than Dr. Katona?

10 DR. SIMON: What would be the proposal? How  
11 would we split -- could you just go through that?

12 DR. PETRI: There would be two separate  
13 questions, one without regard to disease severity and one  
14 without regard to prior DMARD use.

15 All right, there are only two people who wanted  
16 to split it, so -- Dr. Hess?

17 DR. HESS: No, I would also. I mean, the  
18 sticking point for me is the phrase "without regard to  
19 disease severity."

20 DR. JAY SIEGEL: Let me say, if some of the  
21 members feel that way, I would very -- I think we would  
22 like --

23 DR. PETRI: Okay, we'll split it. It sounds  
24 like at least four.

25 So B, Part 1, "As monotherapy in patients with

1 active RA without regard to disease severity."

2 Dr. Katona?

3 DR. KATONA: Since I'm the first one, can I  
4 just define what a yes or a no is going to mean?

5 DR. PETRI: Yes means you agree with the  
6 statement Enbrel can be used as monotherapy in patients  
7 with active RA without regard to disease severity. Do you  
8 agree?

9 DR. KATONA: No.

10 DR. PETRI: Dr. Goldsby?

11 DR. GOLDSBY: No.

12 DR. PETRI: Ms. Malone?

13 MS. MALONE: No.

14 DR. PETRI: Dr. Harris?

15 DR. HARRIS: No.

16 DR. PETRI: Dr. Frieri?

17 DR. FRIERI: No.

18 DR. PETRI: Dr. Yocum?

19 DR. YOCUM: No.

20 DR. PETRI: Dr. Simon?

21 DR. SIMON: No.

22 DR. PETRI: Dr. Luthra?

23 DR. LUTHRA: No.

24 DR. PETRI: Dr. Liang?

25 DR. LIANG: No.

1 DR. PETRI: Dr. Tilley?

2 DR. TILLEY: No.

3 DR. PETRI: I vote no.

4 Dr. Abramson?

5 DR. ABRAMSON: No.

6 DR. CALLAHAN: No.

7 DR. PETRI: Sorry. Dr. Callahan said no.

8 Dr. Hess?

9 DR. HESS: No.

10 DR. PETRI: Dr. White?

11 DR. WHITE: No.

12 DR. PETRI: Dr. Pucino?

13 DR. PUCINO: No.

14 DR. PETRI: Dr. Felson?

15 DR. FELSON: No.

16 DR. PETRI: So that's unanimous.

17 Now we have to do B, Part 2, "As monotherapy in  
18 patients with active RA without regard to prior DMARD use."

19 Dr. Katona?

20 DR. KATONA: Yes.

21 DR. PETRI: Dr. Goldsby?

22 DR. GOLDSBY: Yes.

23 DR. PETRI: Ms. Malone?

24 MS. MALONE: Yes.

25 DR. PETRI: Dr. Harris?

1 DR. HARRIS: Yes.  
2 DR. PETRI: Dr. Frieri?  
3 DR. FRIERI: Yes.  
4 DR. PETRI: Dr. Yocum?  
5 DR. YOCUM: No.  
6 DR. PETRI: Dr. Simon?  
7 DR. SIMON: No.  
8 DR. PETRI: Dr. Luthra?  
9 DR. LUTHRA: No.  
10 DR. PETRI: Dr. Liang?  
11 DR. LIANG: No.  
12 DR. PETRI: Dr. Tilley?  
13 DR. TILLEY: No.  
14 DR. PETRI: I vote no.  
15 Dr. Abramson?  
16 DR. ABRAMSON: No.  
17 DR. PETRI: Dr. Callahan?  
18 DR. CALLAHAN: Yes.  
19 DR. PETRI: Dr. Hess?  
20 DR. HESS: No.  
21 DR. PETRI: Dr. White?  
22 DR. WHITE: No.  
23 DR. PETRI: Dr. Pucino?  
24 DR. PUCINO: No.  
25 DR. PETRI: Dr. Felson?

1 DR. FELSON: No.

2 DR. PETRI: Okay. So the nos have that vote.

3 Now let's go on to Part C, which is, "As part  
4 of combination therapy with methotrexate." Then there's a  
5 subpart here, "If yes, should the use of Enbrel in  
6 combination with methotrexate be limited to patients who  
7 are failing (please define) methotrexate?"

8 I'm very willing to start this discussion. I'm  
9 not sure what "failing methotrexate" should ever mean, but  
10 if someone's on methotrexate and they have an ACR 20  
11 response, and they have a chance to have an ACR 70 response  
12 with Enbrel, I would be very willing to add it. But let me  
13 just throw that on the table for others to agree or  
14 disagree.

15 Dr. Silverman?

16 DR. SILVERMAN: I agree with that statement  
17 about the failure, but my only concern, again, comes back  
18 to infection. If we were concerned about the potential for  
19 serious infection and/or malignancy with Enbrel without  
20 methotrexate, once you add in another medication, which we  
21 know is going to increase risk, particularly in the face of  
22 corticosteroids, I think the data just isn't shown for its  
23 safety.

24 DR. PETRI: Dr. White?

25 DR. WHITE: My view of the data, as I said

1 before, is that there are inadequate safety data to allow  
2 me to feel comfortable making much of a risk/benefit  
3 judgment. Moreover, the efficacy data don't convince me  
4 that the combination is better than the drug by itself in  
5 the same group of patients.

6 DR. PETRI: Dr. Felson?

7 DR. FELSON: Boy, for the first time today,  
8 Barbara, I'm going to disagree with you. I've really liked  
9 absolutely everything you've said up until now.

10 I was pretty convinced by the combination trial  
11 with the 2:1 randomization scheme of methotrexate versus  
12 combination methotrexate/Enbrel with respect to efficacy.  
13 I think it sounds like we're pretty much all in agreement  
14 that the safety data here is wanting. But they showed very  
15 highly significant efficacy parameters -- I mean,  
16 remarkable efficacy of the combination versus 20 to 22  
17 percent ACR response in the methotrexate group.

18 DR. WHITE: That's not the point I'm arguing.  
19 The point I'm arguing is, is that different than Enbrel  
20 alone or Enbrel plus methotrexate, and if they're not  
21 different, which I remain totally unconvinced of, then why  
22 give them together? We also teach people not to do that.

23 DR. FELSON: But I think this is a question of,  
24 do you add Enbrel to someone who's a partial responder to  
25 methotrexate, a la the important cyclosporin trial that did

1 this, and I'm sure this trial is designed similarly, a  
2 partial responder to methotrexate. Now, should we in our  
3 labeling allow for the possibility that somebody's already  
4 on methotrexate, has some response to it, so that you don't  
5 want to necessarily take them off, and yet you would expect  
6 that they would do even better if they had Enbrel added?  
7 And I think the trial suggests that that's reasonable in  
8 terms of efficacy. I can't speak to its safety, but --

9 DR. WHITE: I think the suspicion is there.  
10 It's not that that's not the tendency of the data, but the  
11 data are very few patients. So to make some sort of a  
12 labeling judgment based on the data as they are, although  
13 they certainly fall in that tendency to meet both  
14 partial --

15 DR. FELSON: Let me just -- I know there are  
16 going to be a lot of comments here, but, Barbara, when  
17 you've got a big effect sometimes, you don't need a lot of  
18 data, and this is a pretty big effect.

19 DR. WHITE: You have no comparison.

20 DR. PETRI: Dr. Yocum, then Dr. Pucino.

21 DR. YOCUM: I actually think they did the study  
22 wrong, and they should have added methotrexate to Enbrel  
23 failures.

24 (Laughter.)

25 DR. YOCUM: The issue here to me is as yet,

1 David, there is a fantastic response, but the response of  
2 Enbrel plus methotrexate appears to be no greater than  
3 Enbrel alone. So do you in fact add a potentially other  
4 toxic drug to a drug that you're already concerned about  
5 safety issues? I guess I would say if it's a partial  
6 response to methotrexate and you're unhappy with it, then  
7 you ought to stop and go on to Enbrel, because, again, I  
8 think the study that should be done is methotrexate to  
9 partial Enbrel responders, and I think the company has said  
10 that themselves, that monotherapy with Enbrel appears to be  
11 as good as combination therapy.

12 DR. PETRI: Dr. Pucino?

13 DR. PUCINO: I would wonder with the FDA,  
14 seeing as there appeared to be a response in the one trial,  
15 blinded trial, that possibly a mandatory Phase IV follow-up  
16 for combination therapy, with approval that if this were  
17 approved as is, that there would be mandatory follow-up.

18 DR. JAY SIEGEL: Of what sort are you --

19 DR. PUCINO: Phase IV surveillance of  
20 combination therapy if this were approved as is.

21 DR. JAY SIEGEL: Surveillance meaning basically  
22 a long-term safety --

23 DR. PUCINO: Long-term safety.

24 DR. PETRI: Several people have not commented.

25 Dr. Luthra, let me ask you.

1 DR. LUTHRA: I think the data that they have  
2 shown in terms of the numbers, if small, did not increase  
3 the toxicity of the two combinations, but, again, we have  
4 really very short-term data, and that's the problem with  
5 the whole presentation, that our safety issues continue to  
6 be worrisome. So right now I have hesitation in accepting  
7 adding Enbrel to methotrexate patients who are partial  
8 responders.

9 DR. PETRI: Dr. Hess, let me ask you.

10 DR. HESS: Well, I was impressed with the data  
11 this morning, because practically all the patients were on  
12 methotrexate, yet they were able to define quite well, I  
13 think, an appropriate response, and if we could come to an  
14 agreement by what you mean by failing methotrexate, I would  
15 see no particular problem, as long as all the other  
16 safeguards are in place.

17 DR. PETRI: I've suggested that failing  
18 methotrexate could include the partial response patients,  
19 because I think very few patients are going to be satisfied  
20 with an ACR 20 response.

21 I think we're probably ready to vote on this.  
22 It's obvious we're not going to have complete agreement.

23 Ms. Malone had a comment.

24 MS. MALONE: I just wanted to ask, when it's  
25 used in combination with methotrexate where the patient is

1 only getting partial response, is the idea of putting them  
2 on Enbrel with the methotrexate to stabilize them or to get  
3 them to reach a better point of activity, et cetera? And  
4 then is the idea to slow down the methotrexate or  
5 eventually eliminate it or try that? What's going to  
6 happen to the levels of methotrexate?

7 DR. PETRI: Hopefully that person, when they  
8 reach ACR 70, someone stops the methotrexate.

9 I don't know if Dr. Weinblatt had a comment.

10 DR. WEINBLATT: I've got a comment since this  
11 trial was a design and a concept that I was particularly  
12 interested in, having taken it from the Tugwell-Pinkus-  
13 Yocum study on cyclosporin, which I should remind the panel  
14 was about 140 patients, of which only 70 received  
15 cyclosporin, so it's about the same number plus or minus 10  
16 patients. The difference was cyclosporin plus methotrexate  
17 versus Enbrel plus methotrexate.

18 I understand the committee's concern about  
19 safety throughout all of this, and I think all of us that  
20 have been here as consultants would share concern about  
21 safety with any trial, but additionally I want to highlight  
22 the issue regarding efficacy with this. When this trial  
23 was set up, it was the clinical impression that we were  
24 interested in finding out whether addition of another  
25 therapy to fairly maximum dose methotrexate in these

1 particular patients would generate an increased clinical  
2 response without increased toxicity in the patients  
3 studied.

4           Sample size calculations were done based upon  
5 the clinical response with the prior Enbrel study, as well  
6 as our knowledge, which had been published regarding the  
7 cyclosporin data, and the methotrexate doses -- and I think  
8 it was already mentioned -- were not insignificant.  
9 Patients generally were on doses between 15 and 25  
10 milligrams per week, which is much higher than we've seen  
11 with any other trial, either by itself or in combination.  
12 So it was basically the state of rheumatology practice as  
13 we know it today.

14           I think we're all aware that rheumatologists  
15 are going to use new therapies in combination with  
16 methotrexate. I think, unfortunately, because of our lack  
17 of ability to generate 100 percent responses with most of  
18 our treatments, we're adding drugs together, and that was  
19 the reason.

20           The randomized trial addressed the issue of  
21 whether the addition of Enbrel induced a better clinical  
22 response seen above that with background methotrexate,  
23 identical design to the Tugwell-Pinkus-Yocum study. In the  
24 long-term study, uncontrolled -- and I want to highlight,  
25 this is not a controlled trial -- we are actually giving

1 the investigator the ability to reduce the dose of  
2 methotrexate over time, and I think that there will be  
3 patients over time that are going to be maintained with 25  
4 milligrams twice a week of Enbrel and a lower dose of  
5 methotrexate for the same clinical response. It's  
6 premature to tell you how low the methotrexate dose is  
7 going to be, and it's premature to state whether we're  
8 going to be able to stop methotrexate. My own bias is that  
9 there are many patients over time that are going to remain  
10 on both drugs to maintain clinical response.

11 DR. PETRI: Dr. Silverman?

12 DR. SILVERMAN: My only concern about it is, as  
13 I look at the data and look at the trials that were done so  
14 far, if I'm reading it right, the initial trials were  
15 methotrexate and/or DMARD failure. There were DMARD  
16 failures, of which many of the patients, if not most, had  
17 failed methotrexate, and they got approximately a 20  
18 percent placebo rate and very similar rates with  
19 methotrexate and Enbrel in this study as they did with  
20 Enbrel alone.

21 I have to agree with Dr. White that I don't see  
22 any evidence that the combination in this group of severe  
23 patients is any better than it was Enbrel alone. If you  
24 look at the placebo in the other group, it's about 20  
25 percent, so it's a little better than placebo and

1 methotrexate, but I don't see that -- it's not comparable,  
2 having the caveat of the other study as a precedent, but  
3 that may not be good precedent.

4 DR. PETRI: Dr. White?

5 DR. WHITE: I would like to ask a question of  
6 the FDA. The sticking point that I have, one of them, is  
7 that in fact there is no head-on comparison of Enbrel alone  
8 with Enbrel plus methotrexate. Does the FDA have any  
9 guidelines when they write combination therapy language  
10 that you would require such a head-on comparison?

11 DR. JAY SIEGEL: In general, when a combination  
12 regimen is used, particularly when it's used for initial  
13 approval of one or more products, we require data usually  
14 from a control arm in the study showing the combination to  
15 be superior to monotherapy. That's a general rule to which  
16 there are exceptions.

17 There have been times, for example, where  
18 combination therapies have been compared to placebo and  
19 shown important benefits on serious morbidity or mortality,  
20 in which there's a reasonable theoretical construct that  
21 both elements of the combination are contributory, in which  
22 we will write a label for use of the combination and seek  
23 in postmarketing information about the individual elements.  
24 That's generally a rarity, because usually drugs aren't  
25 developed that way, and that's probably generally good.

1                   It's good to compare comparisons with  
2 individual agents, but there's not a hard rule in that  
3 regard, nor is there a strong or solid, hard precedent in  
4 our labeling as to how explicit we are, particularly in the  
5 indications section, as to which combinations are or are  
6 not acceptable. Where there are particular concerns about  
7 the safety or efficacy of use of combinations that have yet  
8 to be studied or have been inadequately studied, we will  
9 sometimes write right into the indication, "Indication  
10 limited to monotherapy" or to specific combinations, but  
11 many other times we're less explicit in the indication, but  
12 in the clinical studies section indicate what data there  
13 are or are not about various potential combinations.

14                   DR. WHITE: One follow-up question.

15                   DR. PETRI: Dr. Weiss had a comment.

16                   DR. WEISS: In answer to, I think, maybe your  
17 more specific question in terms of what's the appropriate  
18 control arm, in this case the combination of Enbrel plus  
19 methotrexate compared to methotrexate alone gives you the  
20 information on what's the added value of Enbrel. What you  
21 were asking about, the combination of Enbrel plus  
22 methotrexate versus Enbrel alone, gives you the opposite,  
23 which is what's the value of addition of methotrexate --

24                   DR. PETRI: Our problem is, there wasn't a  
25 three-arm study, so we're sort of stuck with what we have.

1 I'm actually going to ask that we vote on this,  
2 because we're getting sort of bogged down here. So Part C  
3 is, can Enbrel be used as part of combination therapy with  
4 methotrexate? We realize the committee has not reached  
5 consensus, but I think it's time for a vote, and I'm going  
6 to start on this side now with Dr. Felson.

7 DR. FELSON: I would vote yes.

8 DR. PETRI: Dr. Pucino?

9 DR. PUCINO: Yes, with the request for Phase IV  
10 follow-up safety data.

11 DR. PETRI: We all want that, so everyone else  
12 does not need to add that.

13 Dr. White?

14 DR. WHITE: No.

15 DR. PETRI: Dr. Hess?

16 DR. HESS: Yes.

17 DR. PETRI: Dr. Callahan?

18 DR. CALLAHAN: Yes.

19 DR. PETRI: Dr. Abramson?

20 DR. ABRAMSON: Yes.

21 DR. PETRI: I vote yes.

22 Dr. Tilley?

23 DR. TILLEY: I don't see data that supports it.

24 DR. PETRI: I think she means no.

25 (Laughter.)

1 DR. PETRI: Dr. Liang?

2 DR. LIANG: Yes.

3 DR. PETRI: Dr. Luthra?

4 DR. LUTHRA: No.

5 DR. PETRI: Dr. Simon?

6 DR. SIMON: Yes.

7 DR. PETRI: Dr. Yocum?

8 DR. YOCUM: No.

9 DR. PETRI: Dr. Frieri?

10 DR. FRIERI: Yes.

11 DR. PETRI: Dr. Harris?

12 DR. HARRIS: No.

13 DR. PETRI: Ms. Malone?

14 MS. MALONE: Yes.

15 DR. PETRI: Dr. Goldsby?

16 DR. GOLDSBY: Yes.

17 DR. PETRI: Dr. Katona?

18 DR. KATONA: Yes.

19 DR. PETRI: So sometimes we don't reach  
20 consensus, but hopefully the controversies are also helpful  
21 to the agency.

22 Now, Part D is perhaps going to be just as  
23 controversial: Can Enbrel be used as part of combination  
24 therapy with other DMARDs? I don't think we have to vote  
25 on hydroxy chloroquine, do we? So I guess we're asking,

1 can it be used with asulfadine and lefludamide?

2 Discussion? Dr. Simon?

3 DR. SIMON: I don't know, and the reason I  
4 don't know is, I don't know. We don't have enough safety  
5 data, we've just spent 15 minutes arguing about a small  
6 study where there was data, and it seems to me that we  
7 can't answer that question with the data that we have.

8 DR. PETRI: Dr. Jeff Siegel?

9 DR. JEFF SIEGEL: Let me just ask you to  
10 clarify that a little bit.

11 (Laughter.)

12 DR. JEFF SIEGEL: Suppose controlled safety  
13 data, with a large number of patients followed a year or 2  
14 years, is provided, which comes out the way it is, which  
15 suggests safety that you would agree indicates safety.  
16 Would you, in addition to that, like to see studies of  
17 combination with each of these agents before you would feel  
18 comfortable recommending its use with those agents?

19 DR. SIMON: So you're hypothesizing --

20 DR. JEFF SIEGEL: I'm not hypothesizing. It's  
21 an ongoing study.

22 DR. SIMON: Yes, but you're hypothesizing that  
23 their data will exist from that ongoing study. We don't  
24 have that data. This is now the third time an ongoing  
25 study has been invoked that exists, yet we don't see it or

1 know it.

2 DR. JEFF SIEGEL: So I'm asking specifically  
3 whether, if there were data like that, you would still like  
4 additional trials.

5 DR. SIMON: I don't know if I'd want additional  
6 trials of hydroxy chloroquine. I don't know. But I would  
7 feel very uncomfortable with drugs that are  
8 immunomodulators, that have evidence of change and  
9 toxicities that are associated with immunomodulation, that  
10 those would not be done in controlled trials. Some of the  
11 drugs, some of what we call DMARDs, don't do that, or at  
12 least we understand, and I would perhaps be a little bit  
13 more comfortable as we gain more experience with this  
14 particular drug in and of itself. So under those  
15 circumstances, I would answer, it depends.

16 DR. PETRI: I actually think -- unless there's  
17 other discussion, I think it's impossible to even vote on  
18 this, because we don't have any data, and I think the  
19 committee as a whole would agree that we'd like to see some  
20 Phase IV data on combinations with other DMARDs,  
21 specifically asulfadine and lefludamide.

22 Dr. White?

23 DR. WHITE: I would also request, I not only  
24 would like -- it depends if you just want to know about  
25 safety. That's a different issue than efficacy. If you

1 actually want to know about efficacy, I would recommend  
2 that it be compared to Enbrel alone, the combination versus  
3 Enbrel alone.

4 DR. PETRI: Dr. Abramson?

5 DR. ABRAMSON: I may just come down on the  
6 minority view here entirely, but I'm more concerned about  
7 seeing more safety data for this drug itself. After that,  
8 I'm more inclined to be rather laissez faire about how  
9 people use it the way we've been mostly with our DMARD  
10 drugs. If other studies want to come out looking at  
11 combinations of cyclosporin and this drug and show that  
12 it's better than other combinations, that's up to the  
13 investigators to do or the company to do. But I wouldn't  
14 set that myself as a bar for them to have to do. Again, I  
15 just want to see more patients with the Enbrel.

16 DR. PETRI: Okay. We're going to discuss Part  
17 E, and then we're going to take a break. So E is, "Please  
18 comment on the responses observed in rheumatoid factor-  
19 negative patients. Should the sponsor be encouraged to  
20 further study this group, such as with other doses or  
21 schedules?"

22 Dr. Yocum?

23 DR. YOCUM: In ways, this speaks back to the  
24 question of severity, and I think there have been a lot of  
25 studies concerning rheumatoid factor-positive and -negative

1 patients and what subpopulations they are. I've expressed  
2 concerns earlier about what rheumatoid factor-positive  
3 patients mean in the pharmacokinetic data that we've seen  
4 and whether rheumatoid factor actually plays a role in  
5 prolonging the presence of this drug. I certainly would  
6 not make it part of labeling or anything else. I think  
7 it's an interesting caveat, but in clinical practice, if  
8 the patient hasn't had a rheumatoid factor and at the  
9 particular point that you decide to test it, it happens to  
10 be negative, and you're going to deny a patient this drug,  
11 I think that would be wrong. But I would like to see  
12 further studies.

13 DR. PETRI: Dr. Felson?

14 DR. FELSON: Yes, I was going to comment that I  
15 think there are two questions here. One is sort of, what  
16 do you think is going on with rheumatoid factor-negative  
17 patients, and the other is, do you think there should be  
18 further study -- forget the phrase "this group" -- do you  
19 think there should be further study, such as with other  
20 doses or schedules?

21 Let me comment on those two questions. What I  
22 think is going on with rheumatoid factor-negative is, I  
23 think, nothing. The same thing that's going on with all  
24 the other patients. I think it's a post hoc subset  
25 comparison that by chance is showing something a little

1 different from all the other subsets, and there were many  
2 that were tested, and one by chance was likely to show  
3 something different. I frankly don't think there is much  
4 there. I think this is likely to be a response like  
5 everything else was a response.

6 DR. PETRI: And let me remind everyone that in  
7 the multiple regression analysis, rheumatoid factor fell  
8 out. So I don't think that this was a big concern.

9 DR. FELSON: That's the answer to number one,  
10 as far as I'm concerned. The answer to number two is a  
11 really different ball of wax, which is, should there be  
12 other -- and it gets to the PK data that was presented  
13 earlier, which was obviously pretty disappointing and  
14 troublesome, and I think that relates to, should there be  
15 other studies with other doses and other schedules? And I  
16 think, boy, the answer to that is underlined and  
17 capitalized yes, with a bunch of exclamation points after  
18 it. I mean, I think that's one of the central troublesome  
19 issues here, that there may be accumulation of this drug,  
20 this may not be the optimal dose or schedule. It's just  
21 not at all clear.

22 DR. PETRI: But you don't mean in rheumatoid  
23 factor-negative patients, you mean in everyone --

24 DR. FELSON: Yes.

25 DR. PETRI: And I think the committee as a

1 whole would echo that.

2 I don't think this requires a vote, and we're  
3 now going to take a 10-minute break. Thank you.

4 (Recess.)

5 DR. PETRI: I need the committee to sit down.  
6 We still have three questions to go, so I'm going to keep  
7 the committee on track.

8 Question 4, "Please comment on data regarding  
9 functional ability and quality of life. To what extent  
10 have beneficial effects been established on disability,  
11 mental health, and vitality?"

12 I want to remind the committee about what  
13 happened when we discussed the lefludamide data, where  
14 there were 1-year data that were very impressive, and the  
15 committee as a whole held them to the 2-year standard to  
16 have an indication for quality of life. There was  
17 disagreement about that, but the committee as a whole voted  
18 to hold lefludamide to the 2-year standard. So I think we  
19 do have to be consistent, but I'm very willing to hear  
20 discussion.

21 Dr. Simon?

22 DR. SIMON: Speaking of consistency, I was not  
23 on the lefludamide panel; however, looking back on what  
24 happened there, I do believe that the invoking of the 2-  
25 year rule had to do with perception of what we didn't know

1 when it was written. We had actually had no data at that  
2 time, and we were then applying what we felt would be a way  
3 to demonstrate significant data that we thought 2 years was  
4 the minimum amount of time that one could accrue data.

5 I think it is important to recognize that as we  
6 accrue more experience, perhaps guidelines are just that,  
7 they should be considered. However, I don't see that we've  
8 seen any data that would actually invoke in this  
9 circumstance an approval or recognition that there is  
10 actually functional data here as we think about it. The  
11 guidelines request not just HAQ, but also SF-36, and I  
12 don't think we've seen any data that supports those  
13 requirements, regardless of the 2-year requirement.

14 DR. PETRI: Dr. Paulus?

15 DR. PAULUS: I hope that the guidelines are in  
16 evolution, because it isn't clear what kind of study design  
17 one should use to show improvement in quality of life and  
18 physical function over 2 years. It probably isn't ethical  
19 to expect to do a placebo-controlled study for that length  
20 of time. One might consider studies where you start with a  
21 6-month trial, demonstrate that you have significant  
22 benefit in 6 months, and then that you can sustain it over  
23 another 18 months of open follow-up, and you approach that  
24 in the data that you have, although the number of patients  
25 who are out to 18 months isn't very many just yet. In

1 terms of physical function as measured by the HAQ, you're  
2 seeing here some very marked improvement, which is  
3 sustained over as long a period as it's been followed. SF-  
4 36 was not really part of the design elements at the time  
5 the trial was started.

6 I think that in terms of this drug, probably we  
7 can't say something about quality of life indication, but  
8 one of the most impressive characteristics of this drug is  
9 that patients have a marked improvement in feeling of well-  
10 being and energy, as the patient described to us before  
11 lunch, and that's something that you don't see with  
12 methotrexate and you don't see with a lot of other  
13 treatments, and we were interested in this vitality index  
14 as a possible reflection of this, which seemed to show  
15 improvement. I think that it would be helpful if some  
16 description of that characteristic of the drug could be  
17 included in the description in the label, and how you go  
18 about doing that, I don't know.

19 DR. PETRI: Let me ask Dr. Jeff Siegel if he  
20 could please just summarize for the committee the quality  
21 of life guidelines to have such an indication.

22 DR. JEFF SIEGEL: I was just talking to Dr.  
23 Karen Weiss and got that. There are two issues here. One  
24 is the claim, which is recognized in the rheumatoid  
25 arthritis guidance document, and this particular claim is a

1 long-term prevention of disability claim, which includes  
2 data on functional status in a 2- to 5-year trial, as well  
3 as data indicating that quality of life is no worse over  
4 that time frame, and hopefully improved. The reason it was  
5 stated that way is that quality of life hadn't been  
6 validated as an index over trials of that length.

7 So I want to say that what we're interested in  
8 getting the committee's feedback on is not just whether  
9 they meet this claim, because clearly they don't have the  
10 2- to 5-year data that's asked for, but the committee's  
11 view about what the data say regarding the different  
12 domains of the quality of life index and what you can say  
13 about the effect of this agent on quality of life.

14 DR. PETRI: Dr. White?

15 DR. WHITE: I would like to say that I think  
16 that durability, as we said in August, is still a major  
17 issue. I haven't changed my mind on that. I think the  
18 guidelines are still appropriate, and I don't think, in the  
19 absence of durability, that the label should say anything  
20 about quality of life, given the data as they are.

21 DR. PETRI: Dr. Liang?

22 DR. LIANG: Well, I'm just impressed with the  
23 effect sizes. I mean, these are really major, and I don't  
24 see why we can't just report what we hear, which is that  
25 there's objective information that standardized scales show

1 profound changes in blah, blah, blah. You can fill in the  
2 blank. I mean, I don't think that that should be omitted,  
3 because it is different. The only other thing that I think  
4 is similar would be prednisone, and in many ways this drug  
5 looks like a very expensive corticosteroid. But I think  
6 that there are very few drugs in our armamentarium that do  
7 this.

8 DR. PETRI: Matt, prednisone is not safe.

9 DR. LIANG: No, no, but it really has a buzz in  
10 terms of vitality, feeling well, reducing joint swelling,  
11 et cetera.

12 (Laughter.)

13 DR. LIANG: We had the same issues, I think.

14 DR. PETRI: Dr. White?

15 DR. WHITE: But, Matt, I think in terms of  
16 consistency, we also felt the data in August were very  
17 suggestive and very supportive of beneficial effects, but  
18 they did not meet the durability issue, and I also would  
19 remind you that I'm certain that we don't have to put that  
20 information in the label. I would guess that Immunex is  
21 quite proud of that data and will make sure that the  
22 general rheumatologist is aware of it. I'm not sure we  
23 need to provide it in the label in the absence of meeting  
24 the standards that we have set.

25 DR. PETRI: I think what's happened is, we have

1 rungs, and you have to have right now a 2-year study for  
2 the quality of life indication. I actually disagree with  
3 that, Jeff, as I think I made very clear during the  
4 lefludamide meeting. I actually think 1 year is  
5 sufficient, and I think Dr. Paulus brought up that some of  
6 the things we right now have in the RA clinical trial  
7 guidelines should be open for discussion and amendment.

8 Dr. Simon?

9 DR. SIMON: I would agree with you, Michelle,  
10 entirely. However, I'm still concerned, and although I'm  
11 not a maven in quality of life issues, and I would defer to  
12 anyone around the table that does health services research  
13 in this regard in commenting on the quality of any one  
14 technology to measure this, but I believe in the context of  
15 these kinds of measurements, that you need more than one  
16 system of measurement to ensure real benefit, and I think  
17 that we may choose to be 1 year or maybe even 6 months, as  
18 Hal suggests, with another 18 months of data as supportive,  
19 but I do think that we need more than one dataset and type  
20 to be able to support the idea.

21 DR. PETRI: Other comments? Dr. Tilley?

22 DR. TILLEY: Just to say that the instruments  
23 they've used, the SF-36, which unfortunately was used in a  
24 very small number of people, is what's considered the state  
25 of the art for generic instruments, and I think those data

1 will be very useful. I wouldn't have a problem with some  
2 comment being made about the quality of life data, with the  
3 caveat that there isn't long-term information.

4 DR. PETRI: The problem, though, with these  
5 indications for labeling is, we've set standards and we've  
6 held other drugs to those standards. That's why I brought  
7 up the lefludamide meeting, because I do think we have a  
8 requirement to be consistent.

9 DR. SWEETERMAN: Dr. Petri, perhaps just one  
10 small clinical --

11 DR. PETRI: Bill, can you just state your name  
12 here?

13 DR. SWEETERMAN: Dr. Sweeterman, CBER. There  
14 is no such thing as a quality of life claim in the  
15 guidelines for the development of products for rheumatoid  
16 arthritis. There's a disability claim, and that involves  
17 assessment of functional status, which is very close to  
18 quality of life in that you use the HAQ and the SF-36, but  
19 per se there is no quality of life claim.

20 DR. PETRI: I stand corrected.

21 Other comments? Let me ask Dr. Weiss, Dr.  
22 Siegel, have we addressed that issue to your satisfaction?

23 DR. WEISS: I guess just a clarification of  
24 whether or not -- oftentimes there's one issue, which is  
25 what is the indication or the claim, and then there are

1 descriptions about the results of the clinical studies,  
2 which includes usually the primary efficacy endpoint, many  
3 of the secondary efficacy endpoints that are felt to be  
4 important, and can the committee give us some guidance on  
5 whether or not some of these aspects of the various  
6 information that came out of the HAQ or the SF-36 should be  
7 described in part of the labeling where we discuss just the  
8 results of the clinical studies?

9 DR. PETRI: I feel uncomfortable about anything  
10 being stated about the SF-36 without knowledge of all the  
11 subscales. Let me ask the other committee members.

12 DR. JAY SIEGEL: Actually, that adds to another  
13 part of the question, which is the subscales. As noted,  
14 there's a lot more data on the HAQ than the SF-36, and as I  
15 understand, though, the HAQ includes in their entirety two  
16 of the subscales, so those who think that comment on the  
17 clinical data might be appropriate would comment on those  
18 scales for which we have a broader database as opposed to  
19 others for which we have less than would perhaps be  
20 appropriate.

21 DR. PETRI: Dr. Tilley?

22 DR. TILLEY: I guess I don't have any problem  
23 with the HAQ data being reported. I mean, it's a well-used  
24 scale in rheumatoid arthritis, and there are two pieces to  
25 quality of life usually, a disease-specific and a generic,

1 and I agree that there's not a lot of -- and SF-36 is the  
2 right generic instrument, but there's not a lot of  
3 information there. But the disease-specific would be fine  
4 to talk about.

5 DR. PETRI: Dr. Simon, then Dr. Silverman.

6 DR. SIMON: In addressing the issue that you  
7 just asked about, putting clinical data in the label or in  
8 the descriptive of the clinical trials section, I think  
9 it's really critical to be consistent in that regard, and  
10 that if indeed discussion goes on at this committee that we  
11 see data that's substantial and that the agency decides to  
12 be selective in what then gets into the clinical trials  
13 descriptive section based on any number of arbitrary  
14 decisions, I'm very concerned about that.

15 So I think that if the discussion is going to  
16 be that the data should be in, it should be good data, and  
17 it should be good data across the board and regularly, and  
18 that there should be criteria for what data get in under  
19 those circumstances if it's not going to be part of the  
20 label, and it should be consistently applied.

21 DR. PETRI: Dr. Silverman?

22 DR. SILVERMAN: I guess my -- having not been  
23 here for lefludamide, I'm wondering if -- I assume the same  
24 discussion came up, and I understand one can adapt, but  
25 it's only a month ago approximately. I'm not sure why the

1 panel would consider not the identical guidelines that were  
2 set out for the previous drug.

3 DR. PETRI: Well, I think Dr. Simon and I, even  
4 though Dr. Simon wasn't there, are saying that we do need  
5 to be consistent. I think every drug has to meet the same  
6 standards to have an indication. Dr. Simon went a little  
7 bit further to say that things shouldn't be part of the  
8 labeling willy-nilly. So you either meet the standards or  
9 you don't.

10 Dr. Hess?

11 DR. HESS: I always have a little bit of  
12 concern about HAQs and the questionnaires, and I'm going to  
13 ask a tangential question to this, which is, I note that in  
14 the studies 75 to 94 percent of the patients were  
15 Caucasians, and I'm presuming that that reflects the set-  
16 up, if you will, or the background of the centers that were  
17 involved in the studies. But it does leave just a little  
18 opening for the statement that the data is to some extent,  
19 at least the HAQs, et cetera, open to some question, if  
20 it's all just one dominant section of the population.

21 DR. PETRI: Dr. Weiss, are you now satisfied?  
22 I think we've run out of things to say.

23 DR. LIANG: Ms. Chairperson?

24 DR. PETRI: Dr. Liang?

25 DR. LIANG: From the written minutes of our

1 meeting where we discussed this, we didn't take a vote on  
2 the issue of the 2-year requirement. We just haggled over  
3 it.

4 DR. PETRI: Well, but there was obviously a  
5 complete lack of consensus, though. Would you agree with  
6 that?

7 DR. LIANG: I can't remember.

8 DR. TILLEY: I just don't remember, either,  
9 that we came down with a specific recommendation against  
10 putting it down.

11 DR. PETRI: All the parts about the committee  
12 not remembering the last meeting are erased from the  
13 minutes of this meeting.

14 (Laughter.)

15 DR. PETRI: Dr. Callahan?

16 DR. CALLAHAN: I just feel like I want to state  
17 that there are numerous studies and data showing the  
18 reliability of the HAQ, and in other populations it has  
19 been demonstrated, and I think it's a very solid instrument  
20 and a good measure here.

21 DR. PETRI: Dr. Simon?

22 DR. SIMON: But alone, Leigh, is it a good  
23 enough measurement?

24 DR. CALLAHAN: I think it measures more than  
25 just functional capacity.

1 DR. SIMON: No, I understand that, but does  
2 it --

3 DR. CALLAHAN: I think it's a broader measure.  
4 I mean, it is not -- I mean, it gets listed in the qualify  
5 of life as the functional component, but I think it's more  
6 generic than being just arthritis-specific, even though it  
7 was developed in arthritis. I think it does have a generic  
8 component, and I think it captures more than just  
9 functional capacity, but they did do the two subscales of  
10 the SF-36 in all of the patients, the mental health and the  
11 vitality.

12 DR. SIMON: Yes, I understand. But do you  
13 think that you would be so bold as to suggest to the FDA  
14 that its guidelines should now be modified, since the  
15 guidelines should be a living document, that with the data  
16 that's been accrued over the last 6 weeks, that maybe we  
17 don't need two techniques, that we don't need a HAQ and an  
18 SF-36, that maybe we could just use one? I just don't  
19 know. I'm asking the question.

20 DR. PETRI: But it's more than that. Are we  
21 saying we need 6 months or a year?

22 DR. SIMON: Well, I was going to get to that  
23 next part in a second. I was wondering about the choice.

24 DR. CALLAHAN: I'm not going to comment on the  
25 guidelines. I'm just commenting that I think what was

1 stated here, we can say there were large effect sizes in  
2 this group. Now, in terms of the labeling of what the  
3 guidelines -- I'm not talking about reorganizing that to  
4 the minute, but --

5 DR. SIMON: But I'm actually asking to learn  
6 something here. I wondered whether or not the preconceived  
7 notions that many of us have that prior to these datasets  
8 that we now have available to us over the last 6 weeks, are  
9 we actually being too stringent applying two different  
10 scalers when we don't need to be?

11 DR. PETRI: Well, I think Dr. Tilley might be  
12 able to help us address this. It's never wrong to have two  
13 scales.

14 DR. CALLAHAN: There's a value in having the  
15 generic and the disease-specific.

16 DR. SIMON: Okay.

17 DR. TILLEY: I guess I feel like we're going  
18 off the point a little here. I think the point is not  
19 whether this should be an indication, I think the issue is  
20 what should be reported on the clinical trial, and I've  
21 heard criticism of other trials where they showed change in  
22 joint swelling and tenderness without showing any  
23 functional change. I think that these data are an  
24 important adjunct to the joint response data, and I think  
25 that in the report on the clinical trial, they should be in

1 there with some indication of the length of time over which  
2 they were collected so that you'd know that this was the  
3 data for such and such months on study medication. But I  
4 think it's an important component of understanding this  
5 drug.

6 DR. PETRI: Dr. White?

7 DR. WHITE: As a point of clarification and  
8 follow-up of Lee's question, you think that should go in  
9 all the package information for all these types of drugs,  
10 not just this drug.

11 DR. TILLEY: I would like that, yes.

12 DR. PETRI: Okay. Now, on to Question 5.  
13 Again, I'm going to ask everyone to read the preamble  
14 themselves. I'll just read the boldface.

15 So 5a, "Should the sponsor be encouraged to  
16 conduct further studies to explore whether a relationship  
17 exists between pharmacokinetic parameters and dose and  
18 schedule, including weight-adjusted versus fixed dose  
19 regimens? Between pharmacokinetic parameters and patient/  
20 disease-related characteristics? If so, which patient/  
21 disease characteristics would be most important to  
22 examine?"

23 DR. YUNG: I was wondering if I could --

24 DR. PETRI: Can you just state your name,  
25 please?

1 DR. YUNG: David Yung from Globamax. I was  
2 wondering if I could kind of give some clarification or  
3 clear up some issues about the pharmacokinetics a little  
4 bit.

5 DR. PETRI: Yes, please.

6 DR. YUNG: Could I have Slide K-20, please?

7 Previously, we talked about the adverse events  
8 of infections and concentrations, and I showed this slide.  
9 That really shows no distinct relationship between the  
10 concentration and the infection with patients who have  
11 infection, which are the circles, and without. They seem  
12 to have the same kind of concentrations. So I don't know  
13 if we can say that there's a direct relationship or  
14 relationship between efficacy and safety and concentration.  
15 I don't think we have that information. In fact, I would  
16 suggest that the information we have is that there is no  
17 direct relationship.

18 Now, I'd like to clear up some issues on the  
19 pharmacokinetics. Could I have Slide K-1? I hope you can  
20 see this. On the right-hand side is the healthy  
21 volunteers, and the half-life is 75. On the left-hand side  
22 is the patients with RA, and the half-life is 104 for those  
23 subjects. Now, you saw previously by Dr. Green there was a  
24 half-life of 171. That half-life occurred because one  
25 subject had a 301-hour half-life. Everybody else had the

1 range of 98 to 115 with RA, and all the volunteers had the  
2 range of 46 to 107. Similar ranges. So the variability  
3 appeared to be comparable between patients with RA and  
4 healthy volunteers, but the half-life appears to be  
5 different.

6 DR. PETRI: What was the number of RA patients  
7 in the single-dose study?

8 DR. YUNG: The single-dose study -- and this is  
9 the unfortunate thing; this is not a typical drug study --  
10 there are only six subjects. So we're not denying that.  
11 But I would like to emphasize something here. What we  
12 really want to know is what's happening in multiple dosing,  
13 though, right? We're not going to single dose our  
14 patients, we're going to multiple dose them.

15 Could I have Slide K-30, please? This is Study  
16 16.0014, so this is one of the efficacy studies in which we  
17 drew blood samples. Blood samples were drawn at Day 21 and  
18 Day 49. Now, unfortunately, the blood samples weren't  
19 drawn all at the same time, so one patient may have a blood  
20 sample drawn at the peak on Day 21 and the trough on Day  
21 49. So we really can't compare those two. What we have to  
22 do is, we have to find concentrations that are at the  
23 comparable same time after dose on Day 21 with the same  
24 time after dose on Day 49.

25 If we do that, that's on the right-hand side

1 here, so it says Day 21, plus or minus 7, Day 49, plus or  
2 minus 7. You can see the line in the box graph is the  
3 mean. So on Day 21 and Day 49, we had the same mean  
4 concentration in all these patients in Study 16.0014, and  
5 that's when you sample the exact same or similar times in  
6 Day 21 and Day 49.

7 Now, if you consider all the concentrations --  
8 i.e., some patients had a trough on Day 49 and a peak on  
9 Day 21, which you know would not be the same -- they should  
10 not be the same -- if you consider all of them, you do see  
11 a statistical difference, and that's on the left-hand side,  
12 Day 21 and Day 49. But you should expect that statistical  
13 difference, because you're sampling at different times,  
14 different intervals. So that's expected. So if we take  
15 similar times on Day 21 and Day 49, we see no difference in  
16 the concentration on Day 21 and Day 49. That means these  
17 patients on Day 21 and Day 49 have to be at steady state.

18 A steady state at Day 21 would result in a  
19 half-life of about 120 hours. A half-life of 120 hours is  
20 about what we saw in the RA patients in the single dose.  
21 That was 104 hours. Not that different.

22 Let me show one more slide.

23 DR. PETRI: Before you show another slide, the  
24 number of patients in this dosing study?

25 PARTICIPANT: There were approximately 45 or 50

1 patients all together. In the selected group, about 20.

2 DR. YUNG: Okay. So about 25 all together on  
3 the left two, and over on this side, on the right, about  
4 20.

5 DR. YOCUM: Why do you have so few dots, then?

6 DR. YUNG: Oh, it's boxed. This is a box plat,  
7 so this is the mean and the quadrant.

8 DR. YOCUM: These were the responders, I'm  
9 assuming.

10 DR. YUNG: No, these are everybody.

11 DR. YOCUM: But we had a dropout at 2 weeks,  
12 right?

13 DR. YUNG: No, this is 0014.

14 DR. PETRI: And in terms of range of weights?  
15 Because one of the issues we're asked to discuss is whether  
16 we should be thinking about weight. So there's a large  
17 range of weights, and adjustment for weight does not change  
18 this.

19 DR. YUNG: No, does not change it.

20 Let's go to K-5, please. Now, this is putting  
21 all our plasma concentrations together from all our studies  
22 at steady state. So you can see the yellows. I can barely  
23 see it. Hopefully, you can see it. The yellows represent  
24 pediatric, and the whites represent adult patients with RA.  
25 And this is across numerous studies. You can see, the

1 first one is about Day 15, and then Day 21, and if you look  
2 across all the way to Day 200, the concentrations, even  
3 though we're talking about different studies, are all about  
4 the same. We've got a band of concentrations. We don't  
5 have all of a sudden a big rise in concentration, even at  
6 Day 200.

7 DR. PETRI: So your only outlier was in the  
8 single-dose study. You have not found an outlier  
9 subsequent to that.

10 DR. YUNG: That's exactly right. So it appears  
11 that our accumulation is predictable.

12 DR. PETRI: Can I ask Dr. Green to respond?

13 DR. GREEN: I think the points in my  
14 presentation were to make that it's a heterogeneous  
15 population, so when you take data and you average it, I  
16 think you tend to lose the individuals who I think may be  
17 different in their pharmacokinetic response. So that's one  
18 issue.

19 Another issue is, half-life has never been  
20 accurately determined either at single dose or with repeat  
21 dosing, 4 or 8 weeks, or during longer periods of study,  
22 such as 6 months or greater. Out beyond 8 weeks, there's  
23 only sparse sampling techniques.

24 And this comes to my last point. The steady  
25 state that is spoken to here is not appropriate for

1 biological molecules, because there are basically two  
2 apparent conditions that might be referred to as steady  
3 state. Large biological molecules have the problem of  
4 permeating tissue membranes, and so at shorter intervals,  
5 let's say up to 3 months, there will be an apparent pseudo-  
6 steady state which is in equilibrium with some tissues, but  
7 not all tissues. It's not uncommon to have large  
8 biological molecules dosed over long periods of time where  
9 the reported half-life can be a few days or even less than  
10 2 weeks, and yet they continue to reach -- when patients  
11 are successively measured at trough levels, they continue  
12 to go up for months, to 3 to 6 months, because it is the  
13 selected barrier that requires time for the passage of  
14 these large molecules to get to these various sites.

15 So to refer to this as a steady state condition  
16 is a misnomer, because we really don't know what that  
17 steady state condition is. We don't have detailed  
18 pharmacokinetics to know where these molecules partition,  
19 and, therefore, the basis for a lot of the statements here  
20 are really unfounded.

21 DR. PETRI: Can you stay at the microphone,  
22 please? Can you educate the committee, what do you feel is  
23 necessary to resolve this issue?

24 DR. GREEN: There are some actions that already  
25 are ongoing. That is, the population PK model is being

1 discussed between FDA and the company, with an attempt to  
2 come to a common agreement as to what is an appropriate  
3 analysis. Nevertheless, I think that a longitudinal study  
4 of patients is necessary to understand what happens -- with  
5 sufficient numbers to understand what happens to those  
6 patients on an individual basis to detail their  
7 pharmacokinetics, because we didn't have time to discuss  
8 here, but there is evidence in the pharmacokinetic data  
9 that was supplied to indicate that there are changes which  
10 there is a disagreement between FDA and the company as to  
11 whether those changes occur and their magnitude.

12 But the bottom line is, we need more data on  
13 individual patients followed successfully over periods of  
14 time, particularly at the 25-milligram dose, which is  
15 intended for approval, so that we understand what  
16 pharmacokinetic situation we're dealing with. So I think  
17 that's the number one issue. And then after that, I think  
18 we would have to see where we are in terms of what the  
19 information tells us.

20 DR. PETRI: Dr. Pucino, then Dr. Abramson.

21 DR. PUCINO: In terms of the one outlier who  
22 had about a 2-week half-life, was there anything unique  
23 about this that could help us use the drug safely in other  
24 patients?

25 DR. YUNG: Yes. In that study, we had a couple

1 of patients in the different arms who -- unfortunately, it  
2 was one patient in one arm and another patient in another  
3 arm, who it looked like maybe a sample was switched between  
4 a placebo group and the non-placebo group. In the other  
5 one, for some reason -- and I don't know the reason -- they  
6 just seemed to have very, very low concentrations, so the  
7 clearance was very fast. That's all we can say.

8 DR. PETRI: Dr. Abramson?

9 DR. ABRAMSON: I just had a question, I guess,  
10 for Dr. Green. In our field, where we use cultracine and  
11 methotrexate and other drugs that plasma levels are not  
12 very relevant to clinical response, or even necessarily to  
13 outcome, why should this issue be important to us today  
14 with respect to the efficacy and safety of this particular  
15 drug?

16 DR. GREEN: I think it's important in part  
17 because this is the first time a biological entity like  
18 this is going to be involved with chronic dosing for as  
19 widespread an indication. So although other models of  
20 drugs in other disease settings may not have been  
21 illuminating in terms of the pharmacokinetic/pharmaco-  
22 dynamic relationship, that doesn't necessarily hold in this  
23 particular case.

24 DR. ABRAMSON: I guess what I'm asking, if you  
25 have 6- and 12-month data of safety and efficacy, how is

1 that going to change based on the pharmaco -- what new  
2 insights will we get that we don't have in terms of  
3 pharmacokinetics?

4 DR. GREEN: Well, I think if the question is  
5 can this be used successfully given safety and efficacy  
6 information, the answer is yes. I think that there is the  
7 opportunity to identify individuals who may be at risk, but  
8 we don't know what that risk is, and, therefore -- and it  
9 may be related to factors which may be readily identified,  
10 short of doing some kind of serial sampling or assessment  
11 at trough. So I think the hope is that you have better  
12 patient management ultimately, once we understand if there  
13 is a pharmacokinetic subpopulation which is different than  
14 the group, and then an attempt to identify them so we can  
15 better manage those patients.

16 DR. PETRI: Let me have a response from Immunex  
17 first. In fact, if I could ask the Immunex response to be  
18 a little bit broader. Does Immunex object to Dr. Green's  
19 suggestion of doing further studies?

20 DR. HAYES: No, we don't object to doing that.  
21 But can I just show one slide to show the question of  
22 efficacy for non-responders versus responders in terms of  
23 levels, or is that relevant?

24 DR. SIMON: I have a question about that slide,  
25 Michelle, before you go.

1 DR. PETRI: Lee, go ahead.

2 DR. SIMON: Well, could we go back to that  
3 slide? I want to thank our esteemed colleague, who  
4 actually assumes that I can understand how to read that  
5 slide.

6 (Laughter.)

7 DR. SIMON: So I want to ask a question about  
8 actually that structure. Is it possible -- I have two  
9 questions. One, I have no idea if 0 to 8 is a wide spread  
10 or a little spread. What does that mean?

11 DR. YUNG: Okay. The variability in the  
12 pharmacokinetics or in the half-life is about 50 to 60  
13 percent across subjects. That's the CV percent.

14 DR. SIMON: Okay.

15 DR. YUNG: Which is, if we talk about other  
16 drugs, you know, intersubject variability of 50 percent is  
17 not unusual. I mean, that's a usual thing. So the  
18 variability that we're talking about occurs with small  
19 molecules as with large molecules, and that's what that  
20 represents.

21 DR. SIMON: Okay. And then if you take a dot  
22 in that first column there on the left and at the bottom,  
23 where it's near zero, and you connected a line to that same  
24 patient 200 days into treatment, is that same dot at the  
25 bottom or does that dot rise?

1 DR. YUNG: If we look at the pediatric group  
2 and we take the similar sampling types, that dot stays the  
3 same -- if you sample 24 hours after the dose, it stays the  
4 same at 24 hours after the dose. Now, unfortunately, not  
5 all the subjects were sampled at the exact same time.

6 DR. SIMON: I understand that. I'm not asking  
7 from 24 hour to 24 hour, I'm looking over 250 days, and the  
8 reason I want to know that is, is it serum albumin or is it  
9 something that actually may be measurably changing in a  
10 person with an active inflammatory disease that may cause  
11 changes in concentration?

12 DR. YUNG: Okay. What I'm referring to is, for  
13 example, in the JRA group, we sampled at 15, 30, and 60  
14 days. We dosed at 15, 30 -- no, we sampled at 15, 30, and  
15 60 days. Twenty-four hours after giving the dose, after  
16 each of those times, the sample would be the same.

17 DR. SIMON: And what about in the adults?

18 DR. YUNG: Same way.

19 DR. SIMON: Same thing. Okay.

20 DR. YUNG: Now, let me qualify that.

21 DR. SIMON: Aha.

22 DR. YUNG: Let me qualify that. I'll qualify  
23 that. Unfortunately, we don't have serial sampling beyond  
24 21 and 49 days.

25 DR. SIMON: Oh, so these aren't the same

1 dots --

2 DR. YUNG: No. This is across --

3 DR. SIMON: So this isn't the same patient.

4 DR. YUNG: This is not the same patient. These  
5 are different studies across.

6 DR. SIMON: I gotcha.

7 DR. YUNG: So we do have for the adults 21 and  
8 49 days, and they're exactly the same.

9 DR. SIMON: But maybe it would be nice to have  
10 250 days in the same patient.

11 DR. YUNG: We don't have that.

12 DR. SIMON: Okay.

13 DR. PETRI: Dr. Hayes, did you want to show  
14 your non-responder versus responder slide?

15 DR. HAYES: Well, it's just the question about  
16 whether we have any evidence that patients did differently  
17 because they had different blood levels. These are just  
18 blood levels that were drawn in responding patients and  
19 non-responding patients at 30 and 60 days. It's a very  
20 crude way of looking at it, it is patient population, but  
21 we have no evidence based on the population kinetics that  
22 responders have any different blood levels than non-  
23 responders. But we certainly have not done serial values  
24 and then saw what the response was.

25 DR. PETRI: Dr. Yocum?

1 DR. YOCUM: Compared to the previous slide,  
2 this is now 2,000. The previous slide was 1 to 8. What  
3 are we looking at?

4 DR. YUNG: Oh, this is 2.4. A different unit.  
5 2.4. Sorry about that.

6 DR. PETRI: Dr. Silverman?

7 DR. SILVERMAN: I have a practical question.  
8 Because the JRA trial was set up that you could be plus or  
9 minus 1 or 2 days, how can you -- even at 30 days and 60  
10 days. Your statement regarding it was taken at the same  
11 time, how was that verified?

12 DR. YUNG: It was taken at the same time after  
13 dose.

14 DR. SILVERMAN: But if they come at different  
15 days and they're dosed on the same day, which was one of  
16 the criteria, they had to be dosed on the same day of the  
17 week all the time, if they come on a different day of the  
18 week, how is your explanation possible?

19 DR. YUNG: This is why not all of the JRA  
20 patients could be included in the dataset. We only  
21 included -- if we look across 24 hours, there was not  
22 statistical difference. But it wasn't all the subjects,  
23 because as you said, some patients came in --

24 DR. SILVERMAN: How many, then? How many do  
25 you have serial samples on, taken at the same time all the

1 time?

2 DR. YUNG: Fifteen.

3 DR. PETRI: I think it's time to summarize the  
4 discussion. Although the panel understands that right now  
5 you don't have any safety or efficacy concerns about the  
6 actual levels of Enbrel, I think Dr. Green's point is that  
7 you need a tighter dataset. I think reasonable people can  
8 hopefully work together, so rather than have this be an  
9 issue of contention, I would urge Immunex to work with Dr.  
10 Green and the agency to resolve this issue. It just takes  
11 a tight dataset.

12 Is there any disagreement among the panel?

13 (No response.)

14 DR. PETRI: So we'll move on to Part B of 5,  
15 "Is the proposed fixed dose appropriate for chronic  
16 treatment in this setting?"

17 Dr. Simon is amused.

18 DR. SIMON: You're asking for my answer?

19 DR. PETRI: Well, we have no data on anything  
20 else.

21 (Laughter.)

22 DR. PETRI: I think the committee as a whole  
23 feels very strongly that as part of Phase IV, we'd like to  
24 see additional studies on, of course, other doses, but  
25 perhaps also different dosing regimens.

1 Dr. White?

2 DR. WHITE: Clarify for me, Michelle, would in  
3 fact dose response studies be part of Phase IV --

4 DR. PETRI: Well, remember that there was a  
5 dose-finding study in Phase I, but we haven't gone beyond  
6 that maximum dose.

7 DR. WHITE: Right, but, Michelle, I thought you  
8 said that in Phase IV we would like to see these, and I'm  
9 not sure how they would be carried out if we're approving  
10 it for fixed dose.

11 DR. PETRI: I think our point is, we can only  
12 approve it for the fixed dose because we have no  
13 information, and I think what we're getting at is what I'm  
14 going to call dose creep, dose escalation. I think we want  
15 to actually discourage rheumatologists from dose creep at  
16 this point, because we have no data about the higher doses.

17 Dr. Hayes, and then Dr. Simon.

18 DR. HAYES: We do plan on doing controlled  
19 trials with other doses and schedules as part of Phase IV.

20 DR. PETRI: Dr. Simon?

21 DR. SIMON: I guess that's why this two-time  
22 suggestion has been evident in CDER before, so that people  
23 would come to this kind of meeting with data that really  
24 shows a broad range of dosages, both from a safety and  
25 efficacy point of view. Perhaps this is not the wisest way

1 to go about evaluating a dose with the data that we have.

2 DR. PETRI: Other comments? Dr. Hess?

3 DR. HESS: Are we talking about 25 milligrams  
4 in the fixed dose? Is this what we mean?

5 DR. PETRI: Correct. Yes.

6 DR. HESS: That's the only one we're  
7 considering?

8 DR. PETRI: Correct. I think that's the only  
9 one we can consider.

10 DR. HESS: And it's the only one that showed  
11 efficacy.

12 DR. SIMON: No, that's not true.

13 DR. HESS: That's why I asked the question.

14 DR. SIMON: But that's the one they suggested.

15 DR. PETRI: Well, I think one of the issues  
16 here in this question is this issue of dose escalation. So  
17 I don't see how we cannot caution that at this point dose  
18 escalation is not appropriate.

19 Dr. Simon?

20 DR. SIMON: And the other side of the coin is,  
21 gee, maybe we should have more data to help us in  
22 understanding whether it's appropriate or not. But until  
23 we have that data, we can't say anything more about it  
24 except we don't know and maybe it's not appropriate.

25 DR. PETRI: I think we would all be very

1 interested in the studies that Dr. Hayes has proposed for  
2 the higher doses, because who knows what the ACR 70  
3 response might be at a higher dose. Again, we understand  
4 that you have to have safety data as well.

5 Dr. Pucino?

6 DR. PUCINO: It would be nice to see more area-  
7 under-the-curve data, particularly if you're doing dose  
8 escalation and you co-model some of the parameters.

9 DR. PETRI: Now we're going to move on to  
10 Question 6. Again, I'm going to ask you to read the  
11 preamble on your own. I'll just read the bold part.

12 So 6a, "Does the committee concur with  
13 inclusion of this type of information in the current  
14 label?," and the information is stated above in terms of  
15 the pediatric rule, and I think Dr. Silverman might like to  
16 start the discussion.

17 DR. SILVERMAN: Well, I think the data to date,  
18 as presented and what I can see, show that this drug  
19 probably works very well in JRA. I don't think there's any  
20 doubt about that. I don't think there's any doubt that  
21 it's an excellent drug for the treatment of polyarticular-  
22 course JRA. I don't think we can make a lot of comments on  
23 the pauci- to poly- individual courses, but that's  
24 irrelevant to the indication.

25 However, what I need clarification on is, we

1 don't have PK data as presented until very recently, like 2  
2 minutes ago on 15 patients, but not even shown, just  
3 stated. So if we need PK data for it, we don't have it.  
4 So despite my introduction of saying it's a wonderful drug,  
5 which I truly believe it is, we cannot say it should go  
6 under the pediatric rule if you require the PK data for it.  
7 The safety data probably could be addressed on an  
8 indication, as we discussed before.

9 DR. PETRI: Dr. Silverman, there is some PK  
10 data from the JRA trial. Do you find that insufficient to  
11 invoke the pediatric rule?

12 DR. SILVERMAN: I find it incomprehensible. I  
13 find I wasn't given it. It may be excellent. I feel today  
14 I have very conflicting data. I have Dr. Green telling me  
15 one thing, I have the company telling me another thing, and  
16 I wasn't privy to make my own decision until 5 minutes ago,  
17 and I didn't see the individual data. So I would have to  
18 withhold judgment on that until I see the individual data.

19 DR. YUNG: Can I make a comment about that?

20 DR. PETRI: Yes.

21 DR. YUNG: As you know, in most pediatric  
22 studies, whether it's small molecules or large molecules,  
23 we're not going to do an intense-sampling typical  
24 pharmacokinetic study.

25 DR. SILVERMAN: No, I understand that, but you

1 have 15 patients, and --

2 DR. YUNG: We actually have like 45 or 50.

3 DR. SILVERMAN: So why weren't we privy to the  
4 data? That's my concern, and that's why I can't comment  
5 without seeing the data. There was a slide that I could  
6 barely see, I couldn't tell the difference between yellow  
7 and white, to be honest, and I had no idea who the 15  
8 patients were. If I would have been provided with that  
9 data, I could have made an intelligent comment.

10 DR. YUNG: Okay. The typical way that we  
11 approach it -- and we approach it through a population  
12 analysis, and as was alluded to before by Dr. Green, there  
13 are some discussions going on about the population  
14 analysis. So all of the children were put into the  
15 population analysis, and, again, because there are  
16 discussions going on between the FDA and the company, we  
17 haven't really shown that. That's really the status.

18 DR. PETRI: I think Dr. Giannini had a comment,  
19 and then Dr. Simon.

20 DR. GIANNINI: I certainly would like to see  
21 the information that we have currently included in the  
22 label, for a couple of reasons. One is, Dr. Siegel's last  
23 couple of slides showed that certainly the efficacy data  
24 appears to be equivalent to that seen in adults. As far as  
25 the safety goes, with the possible exception of the GI

1 symptoms, that appears to be similar. As I mentioned  
2 before, the issue of the aseptic meningitis following the  
3 varicella just can't be resolved, and if you look at a  
4 standard text, such as Figan's "Infectious Disease in  
5 Kids," it will say that those symptoms do occur now and  
6 then in children with varicella infection. So whether or  
7 not it was causative, we just can't say.

8           The second reason -- and perhaps more important  
9 -- is that when this drug becomes available, pediatric  
10 rheumatologists are going to prescribe it. They are not  
11 going to wait for an official indication for JRA.  
12 Certainly it would be nice to include in the label some  
13 information to the pediatric rheumatologists in terms of  
14 dosing and in terms of the safety that we saw in this  
15 study.

16           Thirdly, it probably would help tremendously  
17 with reimbursement from managed care organizations.

18           But for those reasons, I think that if the PK  
19 data could be considered sufficient -- and granted we do  
20 have some safety data, perhaps not enough -- then it seems  
21 like this would be an ideal candidate for inclusion under  
22 the pediatric rule.

23           DR. PETRI: Let me ask Dr. Silverman if you're  
24 willing to compromise on this, because we, I think, readily  
25 accept that we're not going to give live viral vaccines to

1 kids on this. If they're infected, we're going to hold it.

2 DR. SIMON: I'm willing to accept pending the  
3 PK data, and to be honest, it looks like it's going to  
4 work. But you're asking me to comment on the pediatric  
5 rule based on PK data that I'm not privy to, on a  
6 population PK study that we haven't seen. So pending that,  
7 a reassurance of the company, which I have no doubt, but I  
8 can't comment directly from personal experience.

9 My other concern is just to rush into it. I  
10 feel that the data available from the withdrawal study will  
11 be available, and as I said, I'm sure this drug is  
12 efficacious, and I'm sure the PK data may not matter as  
13 addressed in the adult. But if it's a requirement for the  
14 pediatric rule, I don't have the data.

15 DR. PETRI: Dr. Simon?

16 DR. SIMON: I have two questions and a comment.  
17 For the company, you've alluded to the fact that there is  
18 an ongoing randomized clinical trial for JRA. That's not  
19 yet done. Is that correct?

20 DR. HAYES: As you saw in the presentation,  
21 this pediatric trial was designed with the FDA to provide  
22 safety data first, and then the efficacy data. So the data  
23 presented today is from the Phase I, Part 1 open-label  
24 safety data. The Part 2, which was the randomization  
25 portion where patients were randomized to placebo or to

1 continue Enbrel, has been completed. The initial analyses  
2 have been looked at, but analysis is continuing of that  
3 data, and it will be filed -- the agency has not yet seen  
4 this data, and it will be filed with CBER by the end of the  
5 year.

6 DR. SIMON: And the second question is that, if  
7 I'm not mistaken, the pediatric rule is predicated on  
8 adequate PK/PD data in the pediatric population as long as  
9 efficacy and safety in the adult is an acceptable bit of  
10 data. Is that not correct? So under those circumstances,  
11 it seems to me that we have an inadequate database to be  
12 able to invoke the pediatric rule in this circumstance.

13 Regardless of how potentially good this drug  
14 may be, here is a situation where in fact I feel I'm being  
15 pressured to do something based on the fact that we're  
16 here, we're convened, we're now, but we don't have a  
17 dataset that actually supports invoking the pediatric rule,  
18 which already was subverting a traditional good way to  
19 determine utility in the pediatric population based on the  
20 difficulties of doing pediatric studies.

21 So, therefore, under those circumstances, I  
22 think that it's inappropriate to invoke the aspect of the  
23 pediatric rule on this dataset, and I do not believe it  
24 should be placed into the label.

25 DR. PETRI: We have some PK data, though. I

1 mean, I have to be very careful here, because some of the  
2 comments make it sound like there's none.

3 Dr. Silverman?

4 DR. SILVERMAN: I think that I agree 100  
5 percent with Dr. Giannini. I would love to have this drug  
6 available. It is efficacious. I think the number of  
7 patients studied is probably adequate to demonstrate that.  
8 The withdrawal study is a bonus, which is not necessary for  
9 the pediatric rule. However, the PK data -- I agree with  
10 Lee that the data is around, it's here. Why are we being  
11 forced to make that decision today when it's an analysis of  
12 data that exists? Can we not defer it for a short period  
13 of time?

14 DR. PETRI: Dr. Katona?

15 DR. KATONA: Since I think we are stuck on this  
16 issue of the PK data, can we ask Dr. Green to comment on  
17 it?

18 DR. PETRI: Dr. Green, could you specifically  
19 address this issue of whether the invoking of the pediatric  
20 rule should wait for additional PK data?

21 DR. GREEN: Let me describe the status of the  
22 PK data with regard to JRA, and maybe that will clarify the  
23 issue. There's common agreement that the rate of clearance  
24 is decreased in children, and that would necessitate some  
25 modification of the dose. The degree to which the

1 modification should occur is unclear because of a  
2 difference in the way the data should be analyzed in the  
3 population PK. So whether there's --

4 DR. PETRI: Your answer, then, is yes. If you  
5 don't know how to adjust the dose in children, you can't  
6 possibly invoke the pediatric rule.

7 DR. GREEN: Then my answer is yes, yes.

8 DR. KATONA: Then my second question is, when  
9 is the next time we can address the pediatric rule about  
10 this drug? What is the mechanism?

11 DR. LIANG: Could I actually ask --

12 DR. PETRI: Dr. Liang?

13 DR. LIANG: Maybe this is going over old  
14 territory, but I was sort of hesitant about that 25-  
15 milligram thing, because the data that we saw today shows a  
16 range of efficacy with a dose relationship. It seems to me  
17 that up to that dose would be a reasonable way to frame it  
18 as well. I mean, some people may only want an ACR 20  
19 response and not a 70. That would allow the little  
20 munchkins --

21 DR. PETRI: I don't have any of those patients.

22 DR. LIANG: I mean, it would give physicians  
23 invitation to adjust the dose according to their gut or  
24 whatever.

25 DR. PETRI: I think physicians already have

1 that ability.

2 DR. LIANG: Okay.

3 DR. PETRI: Dr. Hayes?

4 DR. HAYES: I would just like, I guess, some  
5 clarification from our point of view about what the  
6 pediatric rule is. We designed a clinical trial to look at  
7 safety and efficacy in pediatrics. We did not come in  
8 requesting to have approval based on no clinical data and  
9 on pharmacokinetics only, and I'm just confused about the  
10 pediatric rule versus actually doing a safety trial, which  
11 we had worked out in terms of numbers, in terms of safety  
12 issues, et cetera, with the agency, not to come in just  
13 with PK data, but to come in with real data. And I would  
14 like to have, I guess, some clarification about --

15 DR. PETRI: Dr. Jay Siegel, could you please  
16 address this? Or Dr. Karen Weiss.

17 DR. WEISS: Actually, I'm a little bit  
18 confused, too, which is why I think it may be worth  
19 spending a little bit of time with this, because Immunex,  
20 again, is to be commended for embarking on this trial. At  
21 the time this application was submitted, we agreed because  
22 the randomized efficacy portion of the trial was not going  
23 to be available at that time, they would submit what data  
24 they had, and indeed, based on the rule that came out in  
25 1994, the agency thought it would be very useful for drugs

1 that were going to be used in pediatric populations for  
2 companies to go out and gather the information that's  
3 available on pediatric use if such information can be  
4 included in the labeling. Not necessarily asking or  
5 allowing for specific indication or claim that safety and  
6 efficacy had been demonstrated in pediatric patients, but  
7 to provide information that is available in pediatric  
8 patients.

9 I think that was the nature of Question 6a,  
10 that we're all under the assumption that once the data are  
11 completely analyzed and should they indicate efficacy in  
12 the randomized withdrawal portion of the study, that that  
13 data will come in, will be reviewed, will be a separate  
14 supplement, will be an amendment to this label that will  
15 include specific indication for pediatric use based on  
16 adequate and well-controlled trials in pediatric patients.

17 But absent that, what we have -- what we're  
18 asking for now is, what should current labeling reflect?  
19 We want to be accurate, and we want to get as much  
20 information out there to practicing physicians who may be  
21 interested in using this agent in pediatric patients even  
22 before we have the information from the randomized  
23 withdrawal study, and I think the view has always been that  
24 more information is always better than less information.  
25 We have a dose that was used, a consistent dose that was

1 used based on a weight-adjusted use in the pediatric  
2 patients, we had information on safety that looked at  
3 somewhat of a comparison with the adult safety information,  
4 and we have the preliminary response in the open-label  
5 portion.

6 So with all that in mind, the question would  
7 be, would the committee feel that information that we have  
8 in hand now, without making any statement that safety and  
9 efficacy have been established, because I think we agree  
10 that it hasn't yet been established -- would that  
11 information be important, informative, useful to have in  
12 current labeling?

13 DR. PETRI: I guess we better get several  
14 agency viewpoints here, and then I'll get back to the  
15 panel.

16 Dr. Jeff Siegel?

17 DR. JEFF SIEGEL: I just wanted to add  
18 something that may not have been clear. The agency isn't  
19 asking whether we should include an indication for children  
20 with juvenile rheumatoid arthritis in the indication  
21 section. That would depend on efficacy data that may be  
22 forthcoming in the blinded efficacy portion of the trial.  
23 What we're asking is whether the information that is  
24 available should be included in the dosing and other  
25 portions of the label.

1 DR. SILVERMAN: But, see, what I don't  
2 understand -- and maybe I'm wrong on the pediatric rule --  
3 is that PK data is required, and maybe the easy way around  
4 all this dilemma is, pending the approval of the FDA,  
5 particularly Dr. Green, that it gets approval of this  
6 committee if the PK data passes muster at the FDA. I think  
7 that everybody could live with that provision.

8 DR. PETRI: Yes, because you have to understand  
9 that the committee is getting confused, because we're  
10 getting different viewpoints from the FDA.

11 Dr. White?

12 DR. WHITE: Help me clarify this. Is there a  
13 specific statement in the pediatric rule that you cannot  
14 include this type of information in the label -- not asking  
15 for indication, but that you cannot include this kind of  
16 information if you do not have PK data?

17 DR. WEISS: I don't believe there is anything  
18 like that in the pediatric rule. The pediatric rule speaks  
19 mainly to extrapolation of efficacy. If the course of the  
20 disease and the drug's effect are felt to be similar, given  
21 the problems of doing controlled efficacy-type trials in  
22 certain pediatric populations, it allows us to say once we  
23 have confirmed efficacy in adult populations that one could  
24 look at data in pediatric populations that may not be.  
25 They can be controlled trials, and that's great, but they

1 don't necessarily have to be randomized, controlled trials,  
2 provided there is adequate information on pharmacokinetics  
3 so that you are comfortable with the dose that you're  
4 recommending, as well as comfortable with the safety  
5 information.

6 DR. WHITE: You don't want -- you're not asking  
7 us to address indication for use in pediatrics, so in fact  
8 we don't have to apply the pediatric rule. And given that,  
9 it is my view that this would be very useful information.  
10 If I were a parent of a child with JRA or if I were a  
11 physician caring for one, I would like to have that  
12 information.

13 DR. PETRI: Dr. Liang, then Dr. Simon.

14 DR. LIANG: I think you can make the case that  
15 they have met and exceeded the pediatric rule. This is no  
16 longer an extrapolation. They're giving you real data on  
17 efficacy.

18 And then this PK thing, I think, is a red  
19 herring. I mean, it's going to come, and there's likely to  
20 be some caveat about revising the dose downward for small  
21 patients. I mean, what else can we do?

22 DR. PETRI: Dr. Simon?

23 DR. SIMON: Well, that's the question, Matt,  
24 what else can we do? And I agree with you that in fact  
25 some of the datasets do exceed that, but Dr. Green has left

1 me with the impression -- and perhaps I'm wrong -- I don't  
2 think we know the right dose. And if that's the case, how  
3 can we possibly even begin to represent the dose?

4 DR. LIANG: But the studies have used the dose.

5 DR. SIMON: That doesn't matter. That may not  
6 be the right dose.

7 DR. GREEN: But I think the question is whether  
8 it's information that's useful, and I think --

9 DR. SIMON: Right. That's my point. My point  
10 is, it's very useful if it describes a dose that's  
11 recommended to be used, because that's what's going to  
12 happen. If it's actually not the right dose based on PK/PD  
13 data, then, therefore, it shouldn't be in the label as a  
14 descriptor.

15 DR. GREEN: Well, I think the question is  
16 really not whether it's the right dose or whether it, in  
17 the framework you're talking about, is perhaps an optimal  
18 dose. It's a dose -- I think what we're aiming for is to  
19 provide information about a dose and its associated effects  
20 as far as we know them in terms of safety. It may not be  
21 an optimal dose, but it may be very well a useful dose.

22 DR. PETRI: I don't think we need to vote on  
23 this. I think the issue is crystal clear to everyone in  
24 the room. Now, we're going to go on to B.

25 Unlike, you know, what's perjury and all that

1 stuff.

2 (Laughter.)

3 DR. PETRI: "If the randomized withdrawal study  
4 indicates efficacy in JRA, what additional data (clinical  
5 or preclinical) should be gathered on use of Enbrel in  
6 pediatric populations -- e.g., effects of Enbrel on growth  
7 and development, antibody response to immunization, host  
8 response to immunization with live viral vaccines, and  
9 experience in children with JRA ages 2 to 4?"

10 Most of these we have previously discussed and  
11 said, of course, we needed information. The one that  
12 surprised me was growth and development. So perhaps I need  
13 to be taught in the committee as a whole, are there any  
14 preclinical concerns about growth and development?

15 Dr. Hayes?

16 DR. HAYES: The data that we have in  
17 preclinical comes mainly from the knockout mice, who have a  
18 total absence of TNF, and these knockout mice have normal  
19 litters, the fetuses grow normally, the infants grow  
20 normally, they grow up, and they're sexually mature, and  
21 they reproduce. And that's in the total absence of TNF.

22 Obviously, the patients on our trial have only  
23 been on for 3-plus months, and the data that you've seen is  
24 only for 3 months, and we can't assess growth in that short  
25 period of time. We will in the long-term study. We're

1 following growth and development. But in the knockout  
2 mice, they grow normally, they develop normally, and they  
3 reproduce normally.

4 DR. PETRI: Dr. Simon?

5 DR. SIMON: Can you induce disease that would  
6 be inflammatory in the knockout mouse?

7 DR. HAYES: I'll ask Dr. Williams to respond to  
8 that.

9 DR. WILLIAMS: I'm Doug Williams from the  
10 preclinical side of Immunex, and, yes, you can induce  
11 disease in the knockout mice, and that's largely due to the  
12 fact that there are redundant cytokine systems which lead  
13 to the development of RA.

14 DR. PETRI: Dr. Silverman?

15 DR. SILVERMAN: I think that I personally have  
16 no problems with growth and development. In fact, one  
17 could argue very strongly the reverse, that as you control  
18 the disease, as you drop prednisone, they would grow  
19 better. I can't think of any true theoretical reason.  
20 However, the only caveat I have is if the knockout mouse  
21 does not have TNF during development, IL-1 could  
22 potentially take over, so there's a caveat in there.  
23 Having said that, I think that it would be actually  
24 excellent for growth and development.

25 DR. GREEN: In terms of the specific studies

1 that were done in reproductive toxicology using the rat and  
2 the rabbit, they don't suggest that there are any problems.  
3 Although they're not long-term studies, they were adequate  
4 studies, and they don't suggest that there is an issue.

5 DR. PETRI: Well, obviously, Immunex is going  
6 to give us information on the growth curves when their  
7 study is completed, so I think that would be sufficient.

8 Dr. White?

9 DR. WHITE: Question, Michelle. The way this  
10 is worded, it implies that we would like to have studies on  
11 the response of children on Enbrel when they are immunized  
12 with live viral vaccines, and I thought we -- I just wanted  
13 to clarify that we don't want that.

14 DR. PETRI: I think it was very clear this  
15 morning that not only do we not want it, we want it in the  
16 labeling that we don't want it.

17 DR. WEISS: There was, I think, a question,  
18 too, about whether that can be done in some other type of  
19 system other than a human being on this agent.

20 DR. PETRI: Dr. Hess?

21 DR. HESS: Just one quickly. I really hadn't  
22 noticed this. That shows how we read these things. But 33  
23 percent of the JRAs who were treated developed  
24 anticardiolipin antibodies within 90 days. Now, we didn't  
25 discuss this when we were discussing autoantibodies. I'd

1 like your comment. I'm scared of the children getting  
2 those things.

3 DR. PETRI: We all remember that there were  
4 problems with the kits. Dr. Hayes, do you want to  
5 rediscuss that?

6 DR. HAYES: That was the data that we showed  
7 you where we reanalyzed all of the pediatric patients with  
8 a single kit and a single lot, and all that noise  
9 disappeared. That was what we showed you, because one-  
10 third of the patients did when we did it with any kit, any  
11 lot, and not batched. When we reanalyzed all of that data,  
12 that's what you saw on that slide. And as you know, there  
13 were no clinical problems with those patients.

14 PARTICIPANT: The final numbers that were  
15 submitted to us were about 5 percent of IgG cardiolipin  
16 antibodies and about 4 percent IgM cardiolipin antibodies  
17 developed during study, which is similar to adults.

18 DR. HAYES: Similar to adults, and were not  
19 sustained.

20 DR. PETRI: Dr. Silverman?

21 DR. SILVERMAN: Can I address the last one, on  
22 experience in age 2 to 4? I would actually put that on a  
23 rather low priority, despite Dr. Katona's comments, mainly  
24 because if you look at the incidence of who gets JRA at  
25 that age group, many are systemics, and we have no

1 indication for children with active systemic disease, and  
2 there's no comment on it, which I would certainly prefer to  
3 see above a study in age 2 to 4, and by the time their  
4 systemic disease burns out, which would make them eligible  
5 for the drug, they're past the age. So I don't think it's  
6 a big issue.

7 I would like to see if the company would  
8 consider a trial with active systemic disease, however, and  
9 I just want to reiterate a statement I made before, and  
10 that was that I think this drug should be used in children,  
11 and I just wish today we had had the PK data for proper  
12 judgment.

13 DR. PETRI: I want to thank all the committee  
14 for their help today, Immunex and their consultants, and  
15 the participants in the audience. Sometimes we get so  
16 bogged down in the safety issues that we forget to say how  
17 enthusiastic we are, and I think everyone on the committee  
18 is extremely enthusiastic about seeing Enbrel being  
19 developed and becoming available to our patients with  
20 rheumatoid arthritis.

21 Thank you all.

22 (Whereupon, at 4:50 p.m., the meeting was  
23 concluded.)

24

25