

1 pharmacovigilance program in place. Over the last
2 three years this program has been expanded to
3 provide a comprehensive picture of safety
4 surveillance.

5 [Slide]

6 The objectives of our pharmacovigilance
7 program are to understand the disease course of RA,
8 particularly in regard to adverse experiences; to
9 attempt to determine relative risk of adverse
10 experiences using prospective and retrospective
11 analyses; to assess adverse events that may have
12 longer latency periods, with longer term
13 observation; and to assess special populations like
14 children, the elderly and those with comorbidities.

15 [Slide]

16 We have supported retrospective studies to
17 better understand rheumatoid arthritis patients.
18 One study, initiated in 1999 by Dr. Gabriel at Mayo
19 Clinic, was to evaluate the epidemiology of
20 infections of rheumatoid arthritis patients using
21 the Olmsted County database. Preliminary results
22 of this population-based study were presented last
23 year at the American College of Rheumatology
24 national meeting. Results from the seminal study,
25 some included in Dr. Wallis' presentation, have

1 established the high rate of serious infections in
2 rheumatoid arthritis patients.

3 [Slide]

4 We are currently engaged with researchers
5 in evaluating linked database analysis of adverse
6 events in RA patients. By tapping into these large
7 insurance claims databases and confirming diagnoses
8 with chart review, the true incidence of adverse
9 events may be determined in actual clinical
10 practices. Furthermore, comparisons can be made of
11 the incidence of these events in etancercept
12 patients and those receiving other DMARD therapies.

13 [Slide]

14 Multiple long-term open-label clinical
15 trials are ongoing in North American and in Europe.
16 Over 1600 patients have been entered in these
17 trials, and include patients with the longest
18 duration of exposure to etancercept, some over five
19 years.

20 [Slide]

21 A number of studies in special populations
22 are ongoing. The first is a study of etancercept
23 in rheumatoid arthritis patients with
24 comorbidities, specifically comorbidities that have
25 been demonstrated the risk of infection. In this

1 1000 patient double-blind, placebo-controlled study
2 etancercept will be added to their background
3 therapy. The first interim analysis was reviewed
4 by a data monitoring board in February of this
5 year, and the study is actively accruing patients
6 at approximately 50 sites. A second study is
7 evaluating etancercept in systemic JRA patients,
8 and there are multiple studies evaluating
9 combination therapy of etancercept with gold,
10 sulfasalazine, or methotrexate.

11 [Slide]

12 Multiple registries have been established
13 to follow more real-world patients. We are
14 currently launching RADIUS. RADIUS stands for
15 rheumatoid arthritis DMARD intervention and
16 utilization study, and consists of two phases. The
17 first phase will include 5000 RA patients from
18 rheumatology practices instituting new DMARD
19 therapies. The second phase will add 5000 RA
20 patients on etancercept. Therapies, comorbidities,
21 clinical status and safety will be monitored.
22 Registries in Europe will include over 5000
23 etancercept patients and over 10,000 comparators.
24 Preliminary data is available on a subset of these
25 patients and the experience reflects what has been

1 seen in clinical trials. A JRA registry has also
2 been established and is currently enrolling
3 patients.

4 [Slide]

5 This comprehensive program illustrates our
6 commitment to proactively evaluate and understand
7 the experience of patients on etancercept. Over
8 13,000 rheumatoid arthritis patients will be
9 followed on etancercept and 19,000 comparators.
10 Long-term experience will allow for the evaluation
11 of potential adverse events that may have longer
12 latency periods, and the real-world experience from
13 observational studies will complement the clinical
14 trial data.

15 [Slide]

16 In summary, the facilitated reporting
17 system allows more complete capture of adverse
18 events. The clinical benefit of etancercept is
19 well established and significant adverse events
20 occur infrequently. After 8 years of study and 3
21 years of commercial experience the risk/benefit
22 profile of etancercept therapy remains strongly
23 positive. Etancercept has helped change the way
24 that physicians approach the treatment of
25 rheumatoid arthritis. We are pleased with the

1 impact that it has had on the lives of patients
2 suffering from this disease. Our responsibility to
3 understand this new therapeutic remains clear as we
4 continue work with the FDA, investigators,
5 physicians and patients.

6 DR. WILLIAMS: We will hold the questions
7 for both sponsors until the question and discussion
8 period. So, we will now turn the time over to
9 Centocor and that will be Jerry Boscia.

10 Centocor Presentation

11 Introduction and Background

12 DR. BOSCIA: Thank you, Dr. Williams.
13 Good afternoon. My name is Dr. Jerry Boscia and I
14 am vice president of clinical research and
15 development at Centocor. On behalf of Centocor, I
16 would like to express appreciation for this
17 opportunity to present information on Remicade or
18 infliximab, with special thanks to Dr. Jeffrey
19 Siegel and Bill Schwieterman for inviting us.

20 [Slide]

21 Remicade is a chimeric monoclonal antibody
22 that is specifically directed against human tumor
23 necrosis factor alpha. I will be giving some
24 background on tuberculosis associated with the use
25 of Remicade and discussing the medical risk

1 management for tuberculosis and other opportunistic
2 infections. Dr. Tom Schaible will then summarize
3 Centocor's plans for communicating these risks and
4 how to minimize them, as well as ongoing and
5 planned studies for better characterizing
6 Remicade's safety profile. I will then present
7 some concluding remarks addressing Remicade's
8 benefit to risk profile.

9 We have a short time to present our
10 information, but in case anyone has additional
11 questions we have with us today several consultants
12 who can help answer any questions. They are, Dr.
13 George Deepe, an infectious diseases,
14 histoplasmosis expert from the University of
15 Cincinnati; Dr. Roy Fleischmann, a rheumatologist
16 from the University of Texas Southwestern Medical
17 Center at Dallas; Dr. Stephen Hanauer, a
18 gastroenterologist from the University of Chicago;
19 Dr. William Shergy, a rheumatologist from the
20 University of Alabama Birmingham, at Huntsville;
21 Dr. Peter Small, an infectious diseases,
22 tuberculosis expert from Stanford University; Dr.
23 Timothy Vollmer, a neurologist from Yale
24 University; and Dr. Frederick Wolfe, a
25 rheumatologist from the Arthritis Research Center

1 Foundation.

2 [Slide]

3 First a little science -- it is important
4 to recognize that a substantial body of data exists
5 establishing the importance of tumor necrosis
6 factor in the response to infectious agents. Tumor
7 necrosis factor is an important mediator of
8 inflammation and cellular immune response.
9 Numerous animal studies have shown that TNF
10 blockade reduces host resistance to certain
11 intracellular pathogens whether this blockade is
12 achieved by neutralizing antibodies or soluble
13 receptors. TNF also plays an important role in
14 macrophage function and granuloma formation, and
15 its blockade may alter the normal granulomatous
16 mechanism for limiting the spread of certain types
17 of infection.

18 [Slide]

19 Since the FDA has already given a
20 comprehensive presentation of the data and the
21 changes made to the prescribing information, I will
22 try not to be too repetitive but, unfortunately, I
23 will have to be a little bit repetitive. It is
24 most important that I discuss the medical risk
25 management so as to minimize the number of cases of

1 active tuberculosis.

2 Centocor has completed 15 clinical trials
3 with Remicade in patients with rheumatoid arthritis
4 and Crohn's disease. An additional 11 trials are
5 ongoing. As of June 30th of this year,
6 approximately 2200 patients have been treated for
7 about 3300 patient years with Remicade in
8 Centocor-sponsored clinical trials. We estimate
9 that 170,000 patients have been treated
10 commercially with Remicade worldwide as of June
11 30th. Approximately 80 percent of these patients
12 are in the United States where Remicade has been
13 available since 1998. The remaining 20 percent of
14 these patients have been treated outside the United
15 States, with the large majority of these in Europe.

16 [Slide]

17 Remicade post-marketing adverse event
18 reporting encompasses several methods. The
19 intravenous infusion of Remicade fosters regular
20 patient and healthcare team interactions. This
21 increases the ability to identify adverse events,
22 and especially serious adverse events, in person.
23 In addition, we have a medical affairs 800 number
24 for healthcare professionals and patients, and a
25 dedicated patient hotline. Our existing website

1 has a MedWatch form that facilitates adverse event
2 reporting directly to Centocor medical affairs and
3 the Food and Drug Administration.

4 [Slide]

5 Remicade has been associated with the
6 occurrence of opportunistic infections, the most
7 significant of these being tuberculosis. As of
8 June 30th of this year, 84 cases of active
9 tuberculosis have been reported worldwide. Three
10 of these occurred in patients in Centocor-sponsored
11 clinical trials and 81 have been reported from
12 post-marketing surveillance. The majority of these
13 cases were pulmonary cases, however, roughly
14 one-third of the reported cases were disseminated.
15 Of 14 deaths, 10 were attributable to tuberculosis.

16 [Slide]

17 The tuberculosis incidence by geographic
18 region is depicted here. Out of 135,000 patients
19 treated in the United States, there have been a
20 total of 20 cases of tuberculosis, for an incidence
21 of 15/100,000 patients. Outside the United States,
22 out of 35,000 patients treated there have been a
23 total of 64 cases of tuberculosis, for an incidence
24 of 183/100,000 patients.

25 [Slide]

1 Of the 15 reports of tuberculosis per
2 100,000 patients receiving Remicade in the United
3 States, the incidence by indication is 19 reports
4 per 100,000 rheumatoid arthritis patients and 8
5 reports per 100,000 Crohn's disease patients. If
6 you remember, when Dr. Lee showed his slide his
7 numbers were 24 and 9, which are very close to
8 these. The reason for the difference is probably
9 the cut-off dates. Dr. Lee's cut-off date was a
10 little earlier in the year this year and ours was
11 June 30th of this year. By comparison, and this
12 has been pointed out by several people this
13 morning, about 6 cases of tuberculosis per 100,000
14 persons are reported in the United States general
15 population.

16 [Slide]

17 A closer examination of the cases of
18 tuberculosis indicates that 50 or 60 percent were
19 reported in patients with rheumatoid arthritis and
20 20 or 24 percent were reported in patients with
21 Crohn's disease. Sixty-two percent of the patients
22 with tuberculosis were women, which reflects the
23 higher proportion of female patients who have
24 rheumatoid arthritis. The mean age of patients
25 with tuberculosis was 54 years. As I mentioned

1 earlier, when looking at the geographic
2 distribution of reported cases, the large majority,
3 that is 76 percent, occurred outside of the United
4 States.

5 [Slide]

6 To summarize this important point,
7 although 80 percent of the patients who have
8 received Remicade are in the United States, almost
9 80 percent of the tuberculosis cases are outside
10 the United States. This suggests that these are
11386X cases of reactivation of latent tuberculosis
12 infection and that this is indicative of the much
13 greater prevalence of latent tuberculosis infection
14 in Europe. Please note that Remicade is the only
15 TNF inhibitor commercially available in Europe
16 without restriction.

17 [Slide]

18 Potential confounding factors for the
19 development of tuberculosis include the fact that
20 rheumatoid arthritis patients being treated with
21 Remicade also receive methotrexate since Remicade
22 is labeled for combination use with methotrexate.
23 Furthermore, patients with rheumatoid arthritis as
24 well as patients with Crohn's disease typically
25 receive other additional immunosuppressive agents

1 such as corticosteroids, azathioprine,
2 6-mercaptopurine and others. Often patients are
3 receiving two or more of these immunosuppressants.

4 [Slide]

5 The time to diagnosis of tuberculosis in
6 Remicade-treated patients also suggests that
7 patients are experiencing a reactivation of latent
8 tuberculosis infection and that if this is going to
9 happen, it happens shortly after commencing
10 Remicade therapy. As shown here, nearly all cases
11 have occurred prior to or at the time of the sixth
12 infusion, which is generally within 7 months of
13 initiating Remicade treatment. The vast majority
14 of cases occurred around the time of the third
15 infusion, which is generally within 6 weeks of
16 initiating therapy, indicated by the spike on the
17 graph. Please note that since January of this year
18 Remicade is the only TNF inhibitor accruing new
19 commercially treated patients without restriction.

20 [Slide]

21 The risk for active tuberculosis should be
22 manageable. Patients should be evaluated for
23 latent tuberculosis infection including, most
24 importantly, tuberculin skin testing by following
25 American Thoracic Society and Centers for Disease

1 Control and Prevention guidelines for the diagnosis
2 and treatment of latent tuberculosis infection.
3 The same recommendations that are outlined for
4 patients receiving immunosuppressive therapy, such
5 as patients receiving the equivalent of greater
6 than or equal to 15 mg/day of prednisone for one
7 month or more should be followed as outlined in
8 those guidelines. If diagnosed, treatment of
9 latent tuberculosis infection should be initiated
10 prior to therapy with Remicade.

11 [Slide]

12 Several opportunistic infections other
13 than tuberculosis have been reported in
14 Remicade-treated patients, mainly through
15 post-marketing surveillance. Very rare cases of
16 histoplasmosis, pneumocystosis, and listeriosis
17 have been reported. The cases of histoplasmosis
18 have all occurred in the Ohio and Mississippi River
19 Valley regions where histoplasmosis is, of course,
20 known to be endemic. For patients who have resided
21 in regions where histoplasmosis is endemic, the
22 benefits and risks of Remicade treatment should be
23 carefully considered before initiation of Remicade.
24 With regard to all of these infections -- all of
25 them -- patients should be monitored for signs and

1 symptoms of infection while on or after treatment
2 with Remicade.

3 [Slide]

4 In summary, since an anti-TNF agent such
5 as Remicade would, due to its mechanism of action,
6 interfere with macrophage function and granuloma
7 formation, it is perhaps not surprising that we are
8 seeing a link between Remicade use and
9 tuberculosis, especially since Remicade-treated
10 patients, for the most part, are already
11 immunocompromised by other concomitant medications.
12 Therefore, when a TNF inhibitor is administered to
13 patients with latent tuberculosis infection
14 reactivation is, indeed, possible.

15 [Slide]

16 Although the overall incidence of serious
17 infections in clinical trials is not greater in
18 Remicade-treated patients than in patients
19 receiving immunosuppressive agents without
20 Remicade, there has been a higher than expected
21 post-marketing rate of reports of tuberculosis.
22 The geographic distribution of cases and the time
23 of onset of tuberculosis, which is early in the
24 Remicade treatment regimen, suggest that we are
25 seeing a reactivation of latent tuberculosis

1 infection. The risk for activate tuberculosis
2 should be substantially reduced by adhering to
3 American Thoracic Society and Centers for Disease
4 Control and Prevention guidelines for the diagnosis
5 and treatment of latent tuberculosis infection.

6 Overall, other opportunistic infections in
7 Remicade-treated patients are very rare, but
8 patients who are considered at high risk for these
9 infections, such as patients who are severely
10 immunocompromised and/or patients who live in areas
11 where such diseases are endemic, should be
12 carefully monitored.

13 [Slide]

14 I would now like to introduce Dr. Tom
15 Schaible, executive director of medical affairs at
16 Centocor, who will walk you through our
17 communication plans regarding the risk management
18 of tuberculosis and our plans for continuing to
19 assess safety in clinical trials.

20 **Communication Plan and Continuing Safety Assessment**

21 DR. SCHAIBLE: Thank you, Jerry. I
22 appreciate this opportunity to talk to the
23 committee.

24 [Slide]

25 In this presentation I will first review

1 our communication plan to physicians and patients
2 regarding the revised labeling on infection risk
3 with Remicade. Second, I will review our ongoing
4 and planned clinical study activities to obtain
5 additional safety information in rheumatoid
6 arthritis and Crohn's disease.

7 [Slide]

8 In addition to the labeling changes to
9 inform physicians about the risk of TB and
10 opportunistic infections, we have also undertaken
11 an active communication plan. This plan will be
12 directed to both healthcare providers and to
13 patients. In addition, the plan will also include
14 a program to measure its effectiveness.

15 [Slide]

16 Key Centocor resources are devoted to the
17 implementation of the communication plan. This
18 includes clinical information scientists, a group
19 of 29 field-based medical affairs personnel who are
20 thoroughly trained in the diagnosis and treatment
21 of TB and other opportunistic infections;
22 immunology specialists, a field force of 273 sales
23 representatives who are also trained in all aspects
24 of the revised labeling and are delivering
25 education materials to physicians using Remicade.

1 With this field force, we will have one Centocor
2 representative responsible for every 30 prescribing
3 physicians. Finally, in addition to our standard
4 response capability, or medical information
5 department has implemented a special call-in number
6 with the capability to fax back information within
7 three hours on the revised labeling.

8 [Slide]

9 Several education materials have been
10 developed to support the communication plan. These
11 include visual guides for physicians and a patient
12 information leaflet. In addition, updated medical
13 information will be available through our website,
14 and a "dear healthcare professional" letter will be
15 mailed to the entire prescribing audience. We
16 understand that physicians do not always read
17 revised labeling information on package inserts.
18 Therefore, we have developed visual guides for
19 physicians to be delivered by our field
20 representatives to enhance the delivery of the new
21 safety information.

22 [Slide]

23 The tuberculosis visual guide is shown
24 here. This is a one-page document, front and back,
25 that summarizes background on TB and the number of

1 cases reported with Remicade on one side, the left
2 side, while the other side summarizes how to
3 evaluate patients for latent TB by skin testing;
4 how to read skin tests; and how to treat patients
5 on the basis of the skin test result, all based on
6 the ATS-CDC guidelines. Copies of this guide are
7 available if you would like to have one.

8 [Slide]

9 The timeline for the roll-out of the
10 communication plan is summarized here. Last week
11 our field representatives were trained and assessed
12 in all aspects of the revised labeling. We
13 targeted 7500 physicians to be visited by our
14 representatives for the specific purpose of
15 reviewing the new safety information with them.
16 These physicians are responsible for treating over
17 90 percent of patients currently receiving
18 Remicade. Approximately 35 percent of these visits
19 have already been completed, and 85 percent will be
20 completed within the next two weeks. The remaining
21 15 percent of targeted physicians will be visited
22 during September.

23 [Slide]

24 The effectiveness of the communication
25 plan will be determined by tracking the number of

1 visits to physicians for purposes of updating them
2 on the revised safety labeling. In addition,
3 quantitative and qualitative research methods will
4 be used to measure awareness and change in
5 screening practices.

6 [Slide]

7 Centocor has been and continues to be
8 committed to obtain prospective long-term safety
9 information in rheumatoid arthritis and Crohn's
10 disease patients who are receiving Remicade. This
11 will be obtained in ongoing Phase III clinical
12 trials, Phase IV clinical trials, patient
13 registries, a long-term safety follow-up program in
14 completed clinical trials, and a case control
15 study.

16 [Slide]

17 Three ongoing Phase III trials are
18 currently being conducted, the ASPIRE trial in
19 patients with early RA receiving Remicade in
20 combination with methotrexate, the ACCENT I trial
21 in patients with active luminal Crohn's disease,
22 and the ACCENT II trial in patients with
23 fistulizing Crohn's disease. ASPIRE has enrolled
24 approximately 700 patients and ACCENT I and II have
25 now completed enrollment. Each of these studies

1 are treating patients with Remicade for one year.

2 [Slide]

3 Three Phase IV studies have been completed
4 or will soon start to collect additional safety
5 information of Remicade in rheumatoid arthritis.
6 One of these, the START trial, has been designed in
7 collaboration with FDA to specifically evaluate the
8 risk of infections in rheumatoid arthritis patients
9 receiving Remicade, and this is the trial that Dr.
10 Siegel described earlier.

11 [Slide]

12 The START trial will evaluate patients
13 with active rheumatoid arthritis despite treatment
14 with methotrexate. One thousand patients will be
15 enrolled at 80 centers in an international setting.
16 Patients will be randomized to 1 of 3 treatment
17 groups, placebo, 3 mg/kg or 10 mg/kg Remicade given
18 every 8 weeks following an induction regimen. As
19 Dr. Siegel indicated, patients in the 3 mg/kg group
20 can be dose escalated if they do not respond to
21 that dose or if they have a flare of disease before
22 the 8-week infusion interval is completed. Placebo
23 patients will be able to crossover to receive
24 Remicade beginning at week 22. Patients will be
25 treated for one year and enrollment will commence

1 in September.

2 [Slide]

3 In addition, the inclusion criteria have
4 been broadened to include patients with rheumatoid
5 arthritis more reflective of patients seen in
6 clinical practice. Therefore, patients with
7 comorbid conditions and/or receiving other DMARDs
8 in combination with methotrexate will be permitted
9 to participate. The primary endpoint of the study
10 will be the proportion of patients who have had a
11 serious infection within the first 22 weeks of
12 treatment. The study has 80 percent power to rule
13 out a 2-fold increase in serious infections.

14 [Slide]

15 Centocor is also currently sponsoring two
16 patient registries to evaluate long-term safety in
17 patients receiving commercially supplied Remicade.
18 One of these registries is in patients with
19 rheumatoid arthritis and the other is in Crohn's
20 disease. The rheumatoid arthritis registry is
21 being conducted by Dr. Fred Wolfe at the National
22 Data Bank for Rheumatic Diseases. Dr. Wolfe's
23 extensive data bank will enable comparison of
24 safety in Remicade-treated patients to a matched
25 control data set. The Crohn's disease registry is

1 overseen by an advisory board of internationally
2 recognized experts in inflammatory bowel disease.
3 This registry is including both patients treated
4 and not treated with Remicade. Both registries are
5 actively registering patients and are targeting a
6 total of 5000 patients each. Currently,
7 approximately 1200 patients are in the Crohn's
8 disease registry and 3100 patients are in the
9 rheumatoid arthritis registry.

10 [Slide]

11 For several years now Centocor has been
12 conducting a long-term safety follow-up program in
13 all patients who have participated in our
14 rheumatoid arthritis and Crohn's disease clinical
15 trials. Patients are followed for death, serious
16 infections, malignancies and new autoimmune
17 disorders for periods 3-5 years following their
18 study participation.

19 [Slide]

20 Finally, we also plan to conduct a
21 retrospective case-control study to explore for
22 risk factors for developing tuberculosis in
23 patients receiving Remicade. This study will
24 compare those patients who developed tuberculosis
25 while receiving Remicade to control patients from

1 the same practice who received Remicade and did not
2 develop tuberculosis. Four matched patients will
3 be selected for each patient who developed
4 tuberculosis, and the data will be analyzed as a
5 matched case-control study.

6 [Slide]

7 In summary, the clinical studies I have
8 reviewed with you will provide safety information
9 on nearly 15,000 patients, and this total does not
10 include the control patients that will be provided
11 by Dr. Wolfe's registry. As you can see, most of
12 these studies are either completed or are ongoing.
13 We believe these ongoing efforts will be invaluable
14 in defining the safety profile of Remicade in
15 rheumatoid arthritis and Crohn's disease.

16 [Slide]

17 In conclusion, Centocor has developed a
18 communication plan about the risk of tuberculosis
19 and opportunistic infections with Remicade. This
20 plan will rapidly educate physicians and patients,
21 and its effectiveness will be measured. We believe
22 this plan will reduce the risk of tuberculosis in
23 patients receiving Remicade. In addition, Centocor
24 will continue its commitment to further
25 characterize the safety profile of Remicade in

1 patients with rheumatoid arthritis and Crohn's
2 disease. This will be accomplished through Phase
3 III and Phase IV studies, patient registries and
4 long-term follow-up programs. In all, these
5 programs will evaluate safety of Remicade
6 prospectively in nearly 15,000 patients with these
7 diseases.

8 [Slide]

9 I would like to thank you for your
10 attention and I would like to return the podium to
11 Dr. Boscia, who will make some comments on the
12 risk/benefit profile of Remicade.

13 **Risk/Benefit Profile**

14 DR. BOSCIA: We are almost done for the
15 morning and early afternoon, folks. I only have
16 three or four more slides. Thanks, Tom.

17 [Slide]

18 Although most of our presentation today
19 discussed risk, I am sure you would agree that no
20 benefit/risk profile can be addressed without some
21 mention of benefit. The ATTRACT trial was a Phase
22 III 2-year study in patients with moderate to
23 severe active rheumatoid arthritis despite
24 methotrexate therapy. After 30 weeks of follow-up,
25 which was the primary endpoint for signs and

1 symptoms, all 4 Remicade treatment regimens in
2 combination with methotrexate produced reductions
3 in signs and symptoms of disease activity as
4 measured by ACR20 criteria. These were
5 significantly greater than the reductions achieved
6 by patients receiving methotrexate alone.

7 [Slide]

8 In ATTRACT, the changes in the Vander
9 Heidi Modified Sharp Score were used to assess
10 progression of structural damage due to rheumatoid
11 arthritis. As shown here, the mean changes from
12 baseline and the total score at week 54, the
13 primary endpoint for structural damage were 0.6 for
14 all 4 of the Remicade dose groups combined and 7
15 for the methotrexate alone group. Thus, there was
16 little or no progression of structural damage
17 observed in the Remicade-treated patients over a
18 period of one year.

19 [Slide]

20 The clinical benefit of Remicade in
21 Crohn's disease is substantial and unique. In this
22 study, which supports our current indication for
23 Crohn's disease, patients who were not adequately
24 responding to conventional therapies were treated
25 with one dose of 5 mg/kg of Remicade. Over 80

1 percent of the treated patients achieved a
2 definitive clinical response, and nearly half
3 achieved clinical remission. The relevance of this
4 benefit is underscored by the low placebo response
5 rates observed. Thus, in Crohn's disease Remicade
6 provides an important clinical benefit and fulfills
7 an unmet medical need.

8 [Slide]

9 In conclusion, Remicade is highly
10 efficacious with regard to signs, symptoms and
11 structural damage in rheumatoid arthritis patients
12 and signs, symptoms and mucosal healing in Crohn's
13 disease patients who have had an inadequate
14 response to conventional therapies. Remicade has
15 been associated with the occurrence of
16 opportunistic infections, the most significant of
17 these being tuberculosis. However, if American
18 Thoracic Society and Centers for Disease Control
19 and Prevention guidelines for the diagnosis and
20 treatment of latent tuberculosis infection are
21 followed, this risk should be substantially
22 reduced. Considering the fact that Remicade is
23 highly efficacious and that the risk for active
24 tuberculosis should be manageable, the benefit to
25 risk profile for Remicade in both rheumatoid

1 arthritis and Crohn's disease continues to be
2 excellent. Thank you all for your attention. We
3 and our consultants will now be happy to answer any
4 questions.

5 DR. WILLIAMS: We would like to thank both
6 Immunex and Centocor for their presentations. We
7 will open it for the committee to ask questions of
8 them both following a break. We will take a brief
9 break and the committee would like to reconvene
10 promptly at one o'clock.

11 [Brief recess]

12 **Questions and Discussion**

13 DR. WILLIAMS: As stated earlier, we have
14 not been given any specific guidelines or any
15 questions to answer. This is for the information
16 of the advisory committee. So, we will now open it
17 to the committee to ask questions of the FDA or
18 either sponsor.

19 DR. VOSE: I had a question regarding the
20 non-Hodgkin's lymphomas. Is there any information
21 regarding the exact clinical histologic subtype of
22 the different lymphomas? That would be helpful
23 with respect to trying to decide if it is from an
24 underlying event or whether it is specifically
25 related to the medication, and also the location

1 perhaps, extranodal sites versus nodal sites of
2 disease.

3 DR. JEFFREY SIEGEL: I think this has been
4 looked at to some extent. I will ask Dr. Braun
5 what information we have about that.

6 DR. BRAUN: Well, this is an area that we
7 are looking at, and we have been collaborating with
8 an investigator at the National Cancer Institute
9 and have amassed a case series of these lymphoma
10 cases. We have also sought additional information
11 from the medical records. I think at this time
12 there aren't any red flags that have popped out
13 about an unusual histologic type that I can tell
14 you about right now, but it is something that we
15 have been working on and we have gathered the
16 information. It is still somewhat in process. We
17 are in the process of preparing this as a
18 scientific analysis or potential publication but at
19 this time I can't say that we have anything
20 striking or unusual about those cases.

21 DR. VOSE: Do you have any idea of how
22 many were aggressive lymphoma versus and indolent
23 lymphoma even with respect to percentages?

24 DR. BRAUN: Again, the best I can tell you
25 is that given the best estimate that we can make of

1 the types of lymphoma you would see in the general
2 population or even in this group, the character or
3 what we know about them so far -- we are still
4 evaluating them but those are good questions and we
5 will be looking at those.

6 DR. ELASHOFF: Both companies have spoken
7 of new safety trials and big registries, but what I
8 would like to know is what is the timeline for some
9 preliminary analyses of the information from those.

10 DR. WILLIAMS: This time I will let
11 Immunex go first and Centocor next. On the next
12 question we will go in reverse order.

13 DR. BURGE: For the registries that we
14 have established, the RADIUS program is just
15 getting initiated right now and the first
16 investigators meeting, actually, is occurring this
17 weekend. So, the 5000 patient RADIUS studies have
18 just been initiated and we will be collecting data
19 on an ongoing fashion, and will be evaluated on
20 interim bases. The European registries -- there
21 are about 1000 patients that are already on study,
22 and we have interim data that we presented at EULAR
23 by the Swedish investigators. Again, as that
24 expands we will be able to update that on a yearly
25 basis.

1 DR. ELASHOFF: When do you expect your
2 first analysis to be done?

3 DR. BURGE: We can do analyses on a
4 routine basis. The plan with the RADIUS program is
5 to be able to provide quarterly updates through the
6 investigators on the information in the program.

7 DR. SCHAIBLE: Both of our registries are
8 currently active so we have 1200 patients in the
9 Crohn's disease registry, 3100 in the RA registry.
10 Now, what we are doing with both of those
11 registries is updates every six months, and we
12 usually time those updates to the key national and
13 international meetings. So, we have already
14 reported results out from the Crohn's registry.
15 Patients in the RA registry just started this
16 January. So, it will probably be another year -- I
17 am looking at Dr. Wolfe, but probably another year
18 before we have a first run of data.

19 DR. WOLFE: The data will be available in
20 the fall for the first 3500, 4000.

21 DR. SCHAIBLE: And for our case control
22 study we will be starting imminently. We are
23 implementing that now.

24 DR. ELASHOFF: And the big safety trial?
25 When is that supposed to be?

1 DR. SCHAIBLE: That starts enrolling in
2 September.

3 DR. ELASHOFF: What is the timeline for
4 that trial?

5 DR. SCHAIBLE: That is a one-year
6 treatment -- I am looking at Dr. Baker --

7 DR. BAKER: It is a 1000-patient trial at
8 80 different sites. So, we are hoping to get it
9 enrolled in a year. We will be monitoring though
10 with data capture in the safety monitoring
11 committee.

12 DR. WILLIAMS: Dr. Callahan?

13 DR. CALLAHAN: I have a couple of
14 questions about the registries and the long-term
15 outcome studies. Are all the data being collected
16 by patient self-report? And, what about patients
17 who are not literate and can't complete
18 questionnaires? Are there efforts being made to
19 recruit those individuals into the study,
20 especially given the fact that tuberculosis is more
21 frequent in populations with lower SES?

22 DR. SCHAIBLE: In the Crohn's registry
23 data is collected both by the physician and from
24 the patient. In Dr. Wolfe's registry, most of that
25 data is from the patient after an initial physician

1 evaluation. Is that correct, Dr. Wolfe?

2 DR. WOLFE: For the registry that we are
3 doing the data are initially collected from the
4 patients and then they are validated by obtaining
5 hospital reports. So, all of the data start from
6 the patients and then are later validated. That
7 turns out to be more accurate because the patient
8 may not go back to the rheumatologist and,
9 therefore, the rheumatologist may not be aware of
10 these events. So, we get them from the patients
11 and then we validate them. We are not making any
12 efforts at this moment in trying to get
13 non-literate patients into this program.

14 DR. SCHWIETERMAN: Mr. Chairman, I think
15 there was some confusion with the microphones, but
16 I didn't hear the Immunex update for the randomized
17 study that you had described, the 1000 patient
18 study with the comorbidities.

19 DR. BURGE: The comorbidities study has
20 accrued just over a quarter of the patients at this
21 point. We had the first data monitoring board
22 meeting in February. After that was reviewed and
23 there were no issues brought up by the committee
24 that reviewed the data, we recruited more sites.
25 We expanded by about 35 additional sites as of

1 June, and they are actively recruiting patients
2 right now.

3 DR. JEFFREY SIEGEL: So that study has
4 recruited a quarter of its patients, and it has
5 been enrolling for how long?

6 DR. BURGE: We initiated the first 17
7 sites about June of last year and the first 100
8 patients were evaluated in February. We recruited
9 them, had to wait 5 months for them to complete the
10 study, get the data in-house, and when everything
11 looked fine we expanded it now so that we can
12 recruit the remainder of the study much more
13 quickly.

14 DR. JEFFREY SIEGEL: So you have 250
15 patients in the first 14 months, but at the current
16 rate of accrual you anticipate finishing accrual
17 when?

18 DR. BURGE: Well, we are hoping to
19 complete accrual in another year.

20 DR. WILLIAMS: Ms. Malone?

21 MS. MALONE: Just a question on how
22 actively recruited are the patients to be on these
23 registries?

24 DR. SCHAIBLE: We are actively recruiting.
25 I will speak to the Crohn's registry and Dr. Wolfe

1 can speak to the RA registry. But, we are actively
2 trying to get more and more patients into the
3 Crohn's registry. I think we have more difficulty
4 there than in the RA registry. I am not quite sure
5 why. But in response, we are actively adding new
6 centers to our registry to increase the number of
7 patients in that registry. I can speak for Dr.
8 Wolfe that since the beginning of the year, since
9 January, 3100 patients have been enrolled in
10 slightly over six months. So, that one is very
11 actively moving along.

12 DR. WOLFE: Yes, we have 3400 patients.
13 We expect to complete the enrollment inside of a
14 year of 5000 patients.

15 DR. BURGE: In regard to the RADIUS
16 registry, we have invited nearly 1000 doctors,
17 hoping to get about 600 to participate and,
18 hopefully, they will contribute their 10-12
19 patients to get the 5000 patient registry accrued
20 very quickly.

21 DR. WILLIAMS: Dr. Callahan?

22 DR. CALLAHAN: I just want to know how
23 many people who were approached agreed to
24 participate.

25 DR. WOLFE: The way the participation

1 works in the registry at this time is that the
2 physicians enroll the patients in their offices at
3 the time they start on Remicade, or they also
4 enroll patients who have already been on Remicade
5 and so far it is about 2 to 1 for new enrollments.

6 This gives me the opportunity to address
7 the other question which is that although the
8 patients consent at this time to participate, as
9 often happens in registries many patients do not
10 wish to continue to participate. But our program
11 will deal with those non-literate and
12 non-participants by actually telephone contact with
13 anyone who has ever registered, and we will
14 continue to follow them by telephone contact as
15 long as we can.

16 MS. MALONE: Just speaking on a personal
17 level without mentioning which of the medications I
18 am involved with, no one has ever approached me
19 about being on the registry and I do take one of
20 the drugs.

21 DR. WILLIAMS: Dr. Katona?

22 DR. KATONA: I would like to ask the
23 particulars of how the patients will be evaluated
24 for the risk of TB, since it is Centocor who is
25 doing it, and in the package insert it is

1 recommended that treatment be initiated. What is
2 the time interval which needs to elapse between the
3 initiation of the treatment with Remicade?

4 DR. BOSCIÀ: Well, I am not sure I
5 understand the first part of your question.

6 DR. KATONA: Let me clarify. Do you
7 recommend both the skin test and the chest x-ray to
8 determine the TB status?

9 DR. BOSCIA: The Centers for Disease
10 Control and Prevention and the American Thoracic
11 Society recommend targeted tuberculin testing, and
12 in this case all people who are going to receive
13 Remicade have to be considered targeted tuberculin
14 testing because they are all going to be receiving
15 something that could predispose them to active TB.
16 As far as the chest x-ray is concerned, the
17 recommendations don't recommend chest x-rays for
18 diagnosing latent TB. Chest x-rays are recommended
19 in everyone who is found to be tuberculin test
20 positive because you have to rule out active
21 tuberculosis before you treat for latent TB
22 because, of course, the treatment for active
23 tuberculosis is much different. Other than that,
24 the only other individuals that I can think of that
25 you would do a chest x-ray in, besides the ones who

1 are tuberculin test positive, are people who are
2 tuberculin negative but have had a close contact
3 with someone with TB because, if they are
4 immunocompromised, you would want to treat them
5 even though they are PPD negative. So, just to
6 rule out active TB, you would do a chest x-ray.

7 DR. KATONA: Can I ask a question just
8 since you have the European experience. On the
9 east coast we have a lot of European immigrants who
10 had BCG. How do you deal with that patient
11 population?

12 DR. BOSCIA: Well, I can answer that for
13 the United States. It is a little bit more
14 difficult in Europe. The CDC/ATS guidelines
15 recommend that you skin test people who have
16 received BCG, and if they are skin test positive,
17 you treat them for latent tuberculosis infection.
18 As you probably know, the reaction wanes over time
19 after you have received BCG.

20 Europe is a completely different story.
21 The guidelines in Europe are different from country
22 to country, and I certainly can't cover each
23 individual country right now. So, I won't. You
24 had a second part to your question, your original
25 question.

1 DR. WILLIAMS: How quickly do you treat
2 the TB?

3 DR. BOSCIA: Well, the way the prescribing
4 information reads right now is that you initiate
5 therapy for latent TB before starting the Remicade.
6 You know, I don't have any data, but for now we
7 feel comfortable with the physician starting the
8 treatment for the latent tuberculosis infection and
9 then starting the Remicade when they feel as though
10 it is clinically okay. In somebody who has active
11 TB, of course, you would not give them Remicade at
12 that point. You would not.

13 DR. WILLIAMS: I would like to ask Dr.
14 Iademarco and Dr. Keane if they have any responses
15 to those questions.

16 DR. KEANE: Yes, I do. I think that the
17 approach taken by the company will serve this
18 problem very well in this country because the way
19 the ATS document and the CDC is constructed, it
20 certainly should prevent a lot of the risk. I
21 think the amount of people who will not be covered
22 by this is concerning, although it may be a very
23 small group of people. They would be people who
24 are anergic, in other words, who just don't react
25 to the test. And this may be 15 or 30 percent of

1 people if they all had tuberculosis infection and
2 still wouldn't react to the test. In this patient
3 group there is the issue of steroid use also
4 preventing the test being positive. In that
5 setting, a chest x-ray won't help you much in terms
6 of diagnosing class 2 TB, which is infection or
7 disease, because the absence of small granulomas or
8 apical capping won't help in that regard.

9 I think my final comment in this regard is
10 that the recommendations of the American Thoracic
11 Society and CDC will deal with this problem as best
12 we can deal with it. Then, we just must be
13 cautious, watching these patients whom we don't
14 treat. We just must be cautious and look out for
15 an unusual presentation of tuberculosis because
16 that is something we have seen here. Most of us
17 looking at TB are used to only 15 percent of
18 patients having extrapulmonary disease and most
19 people come in with pulmonary, straightforward TB.
20 That is not the profile we have been seeing here.
21 So, we just must be cautious about unusual
22 presentations of tuberculosis.

23 In terms of the assessment of these
24 people, which the company has already referred to,
25 they all get PPD tests. They may not, in fact, be

1 at increased risk, some of them. They may be on
2 low dose steroids and they may come from an opulent
3 part of the country where TB is very unlikely, but
4 they are high consequence and that has to be part
5 of the reason why the company insists why this is
6 done. That is just my comment on that.

7 DR. IADEMARCO: I agree with the technical
8 details as presented in the last several comments.
9 I would like to just comment from a broader
10 perspective, and that is that although we are here
11 today focused on several products related to
12 tuberculosis disease as an adverse event, there
13 really is a larger, more important group and that
14 is patients with rheumatoid arthritis and Crohn's
15 disease, who are immunosuppressed in general, who
16 are at higher risk for TB. This was pointed out in
17 the presentations.

18 So, I tend not to focus on these
19 particular products but on this other, larger
20 category. When you consider that "larger category"
21 from a national perspective, it is a very small
22 category. So, the recommendations from ATS and CDC
23 that have been quoted are focused on yet a larger
24 picture. So, a lot of the technical details that
25 have been mentioned and the confounding or

1 complicating factors I agree with that have been
2 mentioned in terms of anergy, BCG, a multitude of
3 other things, there might be some usefulness in
4 trying, for the interested parties, to pursue -- I
5 don't necessarily want to say consensus but further
6 think in an in-depth way about a rational, more
7 uniform screening approach. Even if that does not
8 occur, some attention to how we communicate this
9 issues as effectively as possible to these types of
10 patients and their healthcare providers around
11 labeling issues, letters that have been mentioned,
12 and also by the corporate world attention to the
13 fostering of collaborations with different academic
14 centers, etc., and even among themselves to get at
15 this I think manageable issue.

16 DR. BOSCIA: Can I just say two things,
17 Dr. Williams, please? I will make it quick. First
18 of all, as far as the anergy point that Dr. Keane
19 brought up, fortunately, the CDC and the ATS
20 lowered the threshold from 10 mm to 5 mm, which
21 helps somewhat but it clearly doesn't cover all
22 patients, but it does help and they should be
23 commended for doing that. *p1406KT was the first
24 thing.

25 The other thing is that the onus is upon

1 us. We have to get physicians who are going to
2 prescribe Remicade, rheumatologists and
3 gastroenterologists, to skin test. We have to.
4 And, if we don't get them to do it, Bill is going
5 to be calling me. You know, we have to do it.
6 Fortunately, it is an isolated -- I may not be
7 saying this correctly, it is an isolated group of
8 individuals and we can get to the rheumatologists
9 and the gastroenterologists. You know, when you
10 talk about some drugs and you talk about
11 idiosyncratic reactions and you have to deal with
12 all kinds of family practitioners and general
13 practitioners, etc., it is a lot more difficult.
14 Here, we have an isolated group that we should be
15 able to get to.

16 DR. WILLIAMS: Dr. Wofsy?

17 DR. WOFSY: I had wanted to address a
18 point on some of the registry kind of issues, but I
19 don't want to interrupt the flow of the
20 tuberculosis discussion either at this point.

21 DR. KEANE: One small addendum, and I look
22 for input from my CDC colleague here, recently we
23 have changed our practice to getting nine months
24 prophylaxis uniformly instead of six. I think that
25 will be probably safe in this situation. The

1 second thing is I said I am optimistic about this
2 program dealing with the problem. Clearly, we will
3 be able to find this out and can I get reassurance
4 in the suggested case-control TB study that we will
5 be able to answer, yes, as I expect things are
6 going fine and this approach is dealing with the
7 problem in this country.

8 DR. WILLIAMS: Dr. Anderson?

9 DR. ANDERSON: I just wanted to ask
10 Centocor -- as you said, it is very important that
11 you communicate with all the rheumatologists, and
12 you said that you would be evaluating the
13 effectiveness of your communication plan, and I was
14 wondering if you could provide some specifics of
15 that.

16 DR. SCHAIBLE: Right, we will be doing
17 several things. First of all, we will be tracking
18 all of the visits to make sure that representatives
19 from Centocor are getting into the offices and
20 talking to the physicians.

21 In addition, we will be doing other things
22 to get information on whether physicians are aware
23 of the revised labeling and whether they are
24 changing their practice for screening patients.
25 So, we have a physician survey that we will be

1 conducting. Part of that will be through the
2 Internet. In addition, we have a program whereby,
3 on a quarterly basis through a third-party
4 organization, selected patient charts are reviewed
5 with the patients identification blinded, to look
6 at those charts to see if physicians are ordering
7 the skin tests. So, that will be a much more
8 quantitative, documentable type of way of measuring
9 the effectiveness.

10 DR. WILLIAMS: Dr. Abramson?

11 DR. ABRAMSON: This is a TB question that
12 is rather broad, so I am not sure to what degree
13 you would want to get into it now, but it speaks to
14 the issue of uniformity of approach. Both of these
15 TNF blockers have warnings about opportunistic
16 infections and tuberculosis. We have different
17 approaches right now, at least as I understand it,
18 between pre-testing, testing for TB with PPD in one
19 instance and not in the other. So, the big
20 question obviously is, is this class effect? Do we
21 take different approaches to the different agents?
22 Do we have enough data to draw any conclusions
23 there? And, how should this be approached in terms
24 of the broad public health issue of going on TNF
25 blockers? Shall we have different strategies for

1 these two agents?

2 DR. WILLIAMS: Well, when you say what do
3 we want to get into, we are determining the agenda
4 from here on out. There are no specific questions
5 from the FDA. So, whatever we want to talk about,
6 we can. Dr. Wofsy?

7 DR. WOFSY: And it turns out that is
8 exactly one of two issues that I wanted to put on
9 the table too with respect to the registries. So,
10 maybe we should follow-up on that a little bit.
11 There are a couple of problems that are very
12 difficult to solve that I think we at least ought
13 to shine some light on. Steve, I think, has
14 started with one of them.

15 So, I would just restate it sort of in the
16 way I was thinking about it, which is that
17 different methodology is being pursued here in
18 these two kinds of long-term follow-ups by each
19 sponsor, and it is really easy to imagine sitting
20 here at some point in the future, trying to look at
21 these apples and oranges and not really being able
22 to sort out some of the questions that are raised
23 by these studies. The obstacles, of course, to a
24 uniform approach are enormous and I am not naive
25 about them, but I think it is worth pointing out

1 that this process would be much better if there was
2 a uniform, coordinated process to collect this
3 information about both of these agents.

4 In a similar vein, let me lay out the
5 other problem that I see, maybe to be informed
6 about, it seems to me there are two kinds of
7 long-term follow-up studies that we have heard
8 about today. One is a sort of more traditional
9 controlled trial with comparator groups where you
10 can compare information. The other is a registry
11 without a comparison group.

12 My question, I guess, applies to both but
13 particularly to the registries that are being
14 developed. That is, I think it is going to be very
15 important if these registries are to be successful
16 at teaching us what we need to know and informing
17 physicians and patients that access to the data is
18 unimpeded. And, I haven't heard anything that
19 would lead me to believe that that is going to be
20 the case.

21 DR. SCHWIETERMAN: Let me answer the first
22 question first about class labeling. Certainly,
23 that option was considered early and was even
24 proposed by one of the sponsors. In this instance
25 and in other instances, the agency very often

1 employs class labeling when there are biological
2 priors, when there is evidence about the effect and
3 when it is relatively likely that a new agent in
4 that particular class is going to cause the same
5 thing. Interferon is a good example.
6 Non-steroidal anti-inflammatory drugs are another
7 example. We have employed some class labeling in
8 effect here with the first modification of each
9 package insert when we started to observe serious
10 infections because we went back to each individual
11 file and looked carefully through all the cases,
12 and through a determination of many different
13 factors, came to the conclusion that it was prudent
14 to put these in.

15 So, the same sort of exercise can be done,
16 and should be done here. I think the reason why we
17 are here this afternoon, discussing this, is to get
18 feedback and input. I mean, clearly there are
19 limitations. One doesn't want to default to class
20 label simply because the mechanism of action
21 happens to have involved the same immunologic
22 primary mediator, in this case TNF. These are two
23 different products that work by different
24 mechanisms, albeit to the same end. So,
25 recognizing that, but also recognizing that they

1 have commonalities as well, I think you simply make
2 a decision based upon what you understand about the
3 mechanisms of action and, even more important,
4 about the data. And, we may be there now -- I
5 don't know -- needing to employ, even from a
6 pragmatic basis, a uniform approach here for the
7 benefit of the patients. So, I guess the short
8 answer is it is data driven and science driven, but
9 it also involves input from experts like you.

10 DR. WILLIAMS: Dr. Jay Siegel?

11 DR. JAY SIEGEL: Yes, I just want to
12 expand on that. I agree with everything Dr.
13 Schwieterman said. On the one hand, I think it is
14 a reasonable presumption that if something occurs
15 with one anti-TNF agent it is a concern that it may
16 well occur with a different anti-TNF agent, and I
17 think we work with that concern and that
18 presumption. I think, on the other hand, there are
19 some data that would suggest that the agents may
20 not be necessarily the same. They haven't been
21 compared head-to-head. It is very hard to tell one
22 way or the other. We also have a number of agents
23 -- I know or at least one -- under study in IND or
24 that have been under study in IND. Different
25 agents have behaved differently in the treatment of

1 sepsis syndrome. Both of these agents were studied
2 with somewhat different results in the treatment of
3 acute sepsis syndrome. That informed some of the
4 earlier labeling decisions. Different agents bind
5 with different affinity, raising issues of the
6 possibility of permanent binding versus binding and
7 re-release and actually transport functions. And,
8 different agents have different in vitro
9 activities. In addition to neutralizing TNF may
10 differ, for example, in ability to fix complement
11 or mediate ADCC.

12 So, there are certainly reasons to be
13 concerned that the effects may all be the same, and
14 there are reasons also to think that they may not
15 be the same, and we look at data with the
16 limitations they have and try to make the right
17 decisions as to when to do something class-wise and
18 when not to. But, often the decisions are based on
19 a fair amount of, let's just say, making the best
20 of limited data rather than on any definitive
21 determinations.

22 DR. WILLIAMS: Dr. Abramson?

23 DR. ABRAMSON: I think that is fair. I
24 guess the question is if one focuses on each of the
25 different potential adverse events and has to take

1 them independently. I guess a concern would be
2 that we are seeing TB signals in each of the
3 products, even some that aren't available yet,
4 enough to put warnings, or at least be a red flag
5 for each of the products. The means of comparing
6 whether one is more likely to do it or not are
7 imperfect means. There are rates per 100,000 of
8 adverse events reporting, and I am not sure that we
9 can say that there is a real difference in the
10 numbers that come out comparing one versus the
11 other, given the limitations of the methodology.

12 So, I think when one looks at a potential
13 mechanism-based effect that is signaling through
14 each of the products, the question then becomes
15 should the treatment of patients be rather much
16 aligned in terms of policies.

17 DR. SCHWIETERMAN: I don't know if there
18 are additional comments. The point is well taken,
19 Steve. As far as access to the registries, well,
20 actually, you know, in many different fora, and now
21 most recently this afternoon, there has been a lot
22 of discussion about collection and analysis of
23 post-marketing adverse event data for these
24 long-term immunomodulatory therapies. I guess I
25 would turn it back to the sponsors, but let me just

1 say that I think that there is no doubt that we are
2 officially in a new era of treatment of rheumatoid
3 arthritis that involves chronic therapy with potent
4 biologic immunomodulators. And, to the extent that
5 we can get a cooperation between the different arms
6 of the government, including CD, NIH, FDA and the
7 sponsors to generate open registries.

8 I think that would be a very good step
9 forward. The devil is in the details obviously,
10 and I don't pretend to think that that is going to
11 be easy, but at least I think we should be talking
12 about that.

13 DR. WILLIAMS: I would like to ask Dr.
14 Vose if she has any comments on the lymphomas that
15 were seen or any concerns.

16 DR. VOSE: Well, that is what I was trying
17 to get a little more information about to make sure
18 that the types of lymphomas were consistent with
19 those that we normally would see in rheumatoid
20 arthritis patients. That information is a little
21 hard to say but, certainly, as far as the overall
22 rate, I think the overall rate of lymphomas is as
23 we would expect in rheumatoid arthritis patients.
24 I don't see that that is increased, but I would
25 still like to see the subtypes in the presentation

1 of patients to be sure it is not unusual in some
2 respect.

3 DR. WILLIAMS: Yes, Dr. Wallis?

4 DR. WALLIS: We have the data on the
5 distribution of proportions of different histologic
6 subtypes of lymphomas from our experience.

7 [Slide]

8 That is on this slide for review. We have
9 compared the cases from the etancercept-treated
10 patients against the background proportions
11 observed in the literature in RA, described by Dr.
12 Kamel from Stanford, and we have, to some extent,
13 felt that the numbers were quite close to the
14 background rates that have been observed in
15 rheumatoid arthritis.

16 DR. VOSE: I think that is very helpful,
17 and I would agree that they look similar to what I
18 would expect. So, I think that is fine.

19 DR. WILLIAMS: So, actually you don't have
20 a lot of concern about them because they didn't
21 show that much increase in frequency.

22 DR. VOSE: No, I think the frequency is
23 what I would expect in a moderately severe
24 rheumatoid population, and with that distribution
25 information I think it is clear that it doesn't

1 appear to change or increase the rate at all.

2 DR. WILLIAMS: Dr. Katona?

3 DR. KATONA: I would like to make an
4 unusual comment since, sitting here through almost
5 every one of these meetings and really seeing the
6 development of these drugs from the beginning, I
7 just have to tell you that I am really impressed by
8 the initiatives of both the companies, as well as
9 the FDA, for all the changes which have happened in
10 the package insert, all the new initiatives which
11 are happening. I think rheumatoid arthritis is a
12 really serious, long-standing, debilitating disease
13 and these are wonderful drugs but they have side
14 effects, and we are learning from that, and I think
15 it is really wonderful and I would just like to
16 encourage all parties, from my personal view, to be
17 as vigilant and just fine-tune all these efforts,
18 but I have just been extremely impressed.

19 DR. IADEMARCO: As was mentioned in the
20 last comment, in terms of there being a lot to
21 learn, although no one wants adverse events, from a
22 scientific viewpoint I have one comment. That is,
23 as I became involved in this process and actually
24 was looking at the different adverse events and
25 different products, it was curious to me, as has

1 been observed by others, that there are subtle
2 differences both in the types of adverse events
3 with regard to tuberculosis and the other diseases,
4 but with regard to tuberculosis, and the mechanisms
5 of action. Globally, tuberculosis is an emergency
6 declared by the World Health Organization, where
7 eight million people have disease every year and
8 two million people die. In the United States,
9 although this is not a huge public health problem
10 and TB is going down continually in the United
11 States, our goal is to eliminate tuberculosis.

12 In coordination with the FDA and the NIH
13 and the CDC, there is an initiative to expand and
14 develop a TB vaccine. So, the focus on these
15 adverse events and trying to figure out exactly
16 what is going on may have a very positive
17 contribution, from a research perspective, in
18 advancing the development of this vaccine. So,
19 anything that can be done by interested parties to
20 pursue this really could fit into a larger positive
21 benefit.

22 DR. WILLIAMS: I have one question I would
23 like to ask Centocor. We heard about demyelinating
24 diseases with etancercept. Have there been any
25 reports of demyelination or demyelinating diseases

1 or exacerbations or demyelinating diseases with
2 infliximab?

3 DR. BOSCIA: Dr. Jeffrey Siegel actually
4 presented the data in his talk. I don't want to
5 steal his thunder, but Jeff mentioned three cases
6 and that is, indeed, what we have in our database.
7 Then, he also mentioned two patients from a
8 clinical trial that had exacerbations on their
9 scans but did not have any clinical activity
10 exacerbations.

11 DR. JEFFREY SIEGEL: I can just add, at
12 the time of the label change, three cases have been
13 reported. At the current time, when we looked
14 again, there were five cases and they were similar
15 in character to the cases I described on
16 etancercept.

17 DR. WILLIAMS: Any further questions or
18 comments?

19 DR. IADEMARCO: Obviously, I could go on
20 forever about TB. My apologies --

21 [Laughter]

22 My comment is that the focus and tone of
23 everything I have heard today really relates to
24 patients and their healthcare providers, a very
25 individual level model. But tuberculosis is a

1 public health problem, and when somebody has TB
2 other people are infected and then progress to
3 disease. So, although I have been impressed with
4 the attention with regard to patient care at this
5 individual perspective, TB is a reportable disease.

6 So, there may be the possibility or
7 opportunity to pay attention to this public health
8 perspective in terms of informing practitioners, in
9 terms of working with local public health
10 departments. I am sure this is on the minds of
11 various individuals in the companies involved. So,
12 this public health perspective with regard to this
13 specific adverse event has additional relevance.

14 DR. WILLIAMS: Dr. Elashoff?

15 DR. ELASHOFF: I just want to say that I
16 think it is extremely important that we get the
17 results of analyses from the safety studies and
18 from the registries promptly and in a timely manner
19 to really address these questions. Otherwise, if
20 things drag on for a long time, then we are not
21 being informed about what is happening.

22 DR. BOSCIA: Dr. Williams, may I?

23 DR. WILLIAMS: Go ahead.

24 DR. BOSCIA: Michael, as far as
25 tuberculosis reports are concerned, hopefully, they

1 are being reported but, of course, as has been
2 pointed out this morning, there is under-reporting
3 that does occur. Most reports though from
4 physicians, from pharmacists, from microbiology
5 laboratories, from other healthcare professionals
6 will make their way to the CDC. Let's put it this
7 way, I have a funny feeling that more reports are
8 getting to the CDC because each one of those
9 individuals -- doctors, infection control
10 practitioners, pharmacists, microbiologists -- are
11 supposed to report to their local authorities, who
12 are then supposed to report to the state, who are
13 then supposed to report to the CDC. They may not
14 be reporting necessarily to the sponsors or to the
15 FDA. It is possible.

16 What I did, Michael, I called down to the
17 CDC and asked them to send to me the form that
18 healthcare professionals are supposed to fill out
19 for each individual case. What I noticed in the
20 five-page form is that concomitant medication is
21 not collected. So, I would like to implore to you
22 -- maybe you could go back down there and collect
23 that data on the form. It would be easy.

24 DR. IADEMARCO: I will comment on two
25 points. One is that I have to point out that

1 although the data moves to the CDC, public health
2 action is local and our efforts are designed to
3 then return that data to local and state health
4 departments where they take appropriate action.
5 So, it really is a very important circle.

6 You allude to various collaborative
7 efforts that could better count or understand some
8 of these issues, and I agree, they need to be
9 explored. The CDC doesn't own the data and we work
10 in cooperation with fifty states, D.C. and all the
11 other territories. So, it is a little complex to
12 negotiate some of these issues but it can be done.

13 Although it sounds potentially easy that
14 one "variable" could be added to our data
15 collection form, in fact, it is quite complicated.
16 Revision to that form occurs every five to seven
17 years. There are various, I guess, bureaucratic
18 issues with getting those forms changed. But your
19 point is well noted because we are in the midst
20 right now, over the next year or two, of revising
21 that form and the input from that will largely come
22 from the fifty states on how to best do that.
23 There are already a number of states that do
24 collect that data, and we can pursue further
25 conversations to identify those states and work

1 with them directly.

2 DR. WILLIAMS: Any further comments or
3 questions? Anything further the FDA would like of
4 us today?

5 DR. SCHWIETERMAN: No, just simply to
6 thank both the sponsors and the committee for this
7 informed and productive discussion.

8 DR. WILLIAMS: Ms. Reedy has a statement
9 before we conclude.

10 MS. REEDY: If you would like us to ship
11 any of your briefing documents to you again, leave
12 them on the table and put your name plate on them.
13 If you would like us to shred them for you, put
14 them on your chair. Thank you.

15 DR. WILLIAMS: Again, we would like to
16 thank the sponsors and the FDA for their
17 presentations.

18 [Whereupon, at 1:50 p.m., the proceedings
19 were adjourned.]

20

- - -