FOOD AND DRUG ADMINISTRATION

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ARTHRITIS ADVISORY COMMITTEE

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TUESDAY,

MARCH 4, 2003

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The above-entitled meeting was convened in the Kennedy Grand Ballroom of the Holiday Inn Silver Spring, 8777 Georgia Avenue, Silver Spring, Maryland, at 9:00 a.m., Dr. Steven B. Abramson, Acting Chair, presiding.

PRESENT:

STEVEN B. ABRAMSON, M.C.	Acting Chair
KATHLEEN REEDY, RDH, M.S.	Executive Secretary
JENNIFER ANDERSON, Ph.D.	Member
SUSAN M. MANZI, M.D.	Member
H. JAMES WILLIAMS, JR., M.D.	Member
WENDY W. McBRAIR, R.N., M.C. C.H.E.S.	Consumer Representative

ARTHRITIS ADVISORY COMMITTEE FDA CONSULTANTS:

STEVEN B. ABRAMSON, M.D.
JANET D. ELASHOFF, Ph.D.
ALLAN GIBOFSKY, M.D., J.D.
NORMAN T. ILOWITE, M.D.
ROBERT W. MAKUCH, Ph.D.

FDA CONSULTANTS FROM OTHER ADVISORY COMMITTEES:

RUTH S. DAY, Ph.D.
DOUGLAS W. BLAYNEY, M.D.
JAMES E. KROOK, M.D.
ELAINE S. JAFFE, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(9:09 a.m.)

CHAIRMAN ABRAMSON: Good morning. I would like to call this meeting of the Arthritis Advisory Committee to order. This meeting is a safety update on the TNF alpha blocking agents. I am Dr. Abramson, NYU and the Hospital for Joint Diseases, and I would like to begin the meeting by having the committee introduce themselves, and begin with Dr. Jaffe.

DR. JAFFE: I am Dr. Elaine Jaffe from the National Cancer Institute, NIH.

DR. KROOK: I'm Jim Krook from a community oncology program in Duluth, Minnesota.

DR. BLAYNEY: I'm Doug Blayney. I'm a medical oncologist from Wilshire Oncology Medical Group in Pasadena, California.

DR. DAY: I'm Ruth Day, Duke University, and I am from the Drug Safety and Risk Management Advisory Committee.

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

DR. MAKUCH: I'm Robert Makuch, head of

biostatistics at Yale University.

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

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

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

SECRETARY REEDY: Kathleen Reedy, Food and Drug Administration.

DR. ILOWITE: Norm Ilowite, pediatric rheumatologist from Albert Einstein College of Medicine.

DR. MANZI: Susan Manzi. I'm a rheumatologist and epidemiologist at the University of Pittsburgh.

DR. GIBOFSKY: Allan Gibofsky, a rheumatologist at the Hospital for Special Surgery and Cornell University in New York.

DR. LIANG: Li-Ching Liang, a medical reviewer at the FDA.

DR. SIEGEL: Jeffrey Siegel, Acting Branch

Chief, Immunology and Infectious Diseases Branch at the FDA.

DR. WEISS: Karen Weiss, Food and Drug Administration.

DR. WOODCOCK: Janet Woodcock. I'm head of Center for Drugs at the FDA.

CHAIRMAN ABRAMSON: Thank you. I would now like to introduce Ms. Kathleen Reedy to read the meeting statement.

SECRETARY REEDY: This meeting statement is for the Arthritis Drugs Advisory Committee on March 4, 2003, a safety update on TNF alpha inhibitors.

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

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

meeting, with the following exceptions.

In accordance with 18 United States Code 208(b)(3) and 505(m)(4), waivers have been granted for the following participants:

Dr. Douglas Blayney for ownership of stock in two of the firms that make TNF alpha inhibitor; each stock is valued between $25,000 and $50,000.

Dr. Allan Gibofsky for ownership of stock in two firms that make TNF alpha inhibitors; one stock is valued between 5 and 25, the other between 25 and 50,000; for consulting for three firms that could be affected by the committee's discussion for which he receives less than $10,000 per firm per year, and for lecturing for three firms that could be affected by the committee's discussions. He receives less than $10,000 per firm per year. Dr. Gibofsky consulting and lecturing is general in nature and is not specific to the products under discussion.

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

Dr. John Cush has been excluded from participating in today's discussions due to his current involvement in studies and past consulting on TNF alpha inhibitors.

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

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

CHAIRMAN ABRAMSON: Thank you. We will begin the meeting with presentations from the agency, from CBER. Just a couple of words on the ground rules. We would like each of the presenters to try and keep to their time frame, because we have an awful lot of important information to cover.

The committee members, at the end of each presentation, will be able to ask a few questions for

clarity, but we would like to leave any general discussion about the area covered to later in the afternoon. But if there are specifics that people want more information on from the presentation, that would be okay.

So I'd like to call on Dr. Siegel, Jeffrey Siegel, to present -- to introduce the topic and the background.

DR. SIEGEL: Thank you very much. Ladies and gentlemen, good morning. In our presentations this morning, the FDA will present a safety and efficacy update on the three approved TNF blocking agents.

The first TNF blocking agent that was approved was etanercept which received approval in 1998. Shortly thereafter, infliximab, or REMICADE, was approved in combination with methotrexate for treatment of rheumatoid arthritis, and just a few months ago in December of 2002 adalimumab, or HUMIRA, was also approved for treatment of patients with rheumatoid arthritis.

Each of these three agents has

demonstrated high ACR, or American College of Rheumatology, response rates of approximately between 45 percent and approximately 60 percent ACR20 responses, and ACR50 and ACR70 responses that have been consistently higher than that seen with placebo.

Some of these studies have been carried out as monotherapy, but many of the studies have also been carried out with combination with background DMARDs or as add-on to methotrexate.

While these products that have shown efficacy, each has also been associated with uncommon but serious adverse events. Etanercept is approved for use as monotherapy or in combination with methotrexate for moderately to severely active rheumatoid arthritis.

I want to point out that, when I say monotherapy, this does not necessarily mean that the product is the only product used for rheumatoid arthritis. Generally speaking, the studies of monotherapy for this agent and others were carried out with patients receiving background low dose corticosteroids and nonsteroidal agents.

Etanercept is approved for improving signs and symptoms of rheumatoid arthritis and for inhibiting the progression of structural damage. Additional indications which etanercept has received include polyarticular-course juvenile rheumatoid arthritis and psoriatic arthritis.

Infliximab is approved for use in combination with methotrexate for moderately to severely active rheumatoid arthritis. The claims are that Infliximab has obtained including improving signs and symptoms of rheumatoid arthritis, inhibiting the progression of structural damage and improvement in physical function, based on a two-year study involving the Health Assessment Questionnaire or HAQ.

Infliximab is also approved for treatment of Crohn's Disease, and in this way it differs from Etanercept. It is indicated for treatment of patients with Crohn's Disease with active disease. In the studies, that was defined as a CDAI score exceeding 220. That is the Crohn's Disease activity index. And Infliximab is also approved for treatment of patients with fistulizing Crohn's disease.

Adalimumab or HUMIRA, as I mentioned, was approved in December of 2002. This is a monoclonal antibody to TNF-alpha. The sequence is entirely human derived. However, studies indicate that HUMIRA does have immunogenicity, as I will touch on a bit more later.

The pivotal trials of Adalimumab assessed its safety and efficacy as monotherapy, in combination with methotrexate, and as add-on treatment to standard of care in a general rheumatology practice situation. It was approved last December.

This slide shows the results of the three large pivotal trials of Adalimumab. The top set of rows shows the results -- Well, one of the studies was as monotherapy. The other was methotrexate combination, and the third study was a study of add-on to standard of care.

As you can see, while it is difficult and problematic to compare across studies, the highest point estimates were seen in the study of methotrexate combination where 63 percent of patients had an ACR20 response, compared to 30 percent with placebo.

Adalimumab was also shown to be efficacious when used as monotherapy and as add-on to standard of care, and here the ACR20 response rates were 46 percent and 53 percent. The ACR50 response rates for methotrexate combination were 39 percent and 22 percent and 29 percent in the monotherapy and add-on to standard of care study. In addition, ACR70 rates higher than placebo were shown.

Adalimumab was approved for use as monotherapy or in combination with methotrexate or other DMARDs for treatment of rheumatoid arthritis. It is approved for improving signs and symptoms of rheumatoid arthritis and for inhibiting the progression of structural damage.

Let me make a couple of points about dosing and administration of Adalimumab. The recommended dose is 40 mg every other week subcutaneously. This dose is the optimal dose for methotrexate combination. However, with monotherapy, 40 mg every other week is efficacious, but higher response rates were seen with 40 mg every week. This was not the case for methotrexate combination, where

higher doses were not more efficacious.

Monotherapy has been associated with higher rates of antibody formation than use with a combination methotrexate. We observed 40 percent antibody formation in methotrexate combination and 12 percent when monotherapy was studied, and immunogenicity is associated with lower ACR response rates.

I am going to turn now to safety update, and this will be the subject of the rest of my presentation and the rest of the FDA's presentations, and this is intended as a follow-up to the comprehensive August 2001 presentation in front of the Arthritis Advisory Committee.

We plan to present an in depth discussion of new data on previously recognized serious adverse events, as well as some newly recognized serious adverse events. We will cover the TB experience with adalimumab, an evaluation of lymphoma, malignancies with all TNF blocking agents, some data on liver injury with infliximab and etanercept, and some data on randomized controlled trials of TNF blocking agents

in congestive heart failure.

The data that you will see is based on a variety of different sources, and this makes the analysis fairly complicated. One source is controlled clinical trials, but a lot of the data is from other sources, including open-label extension studies. And I want to mention here that each of the companies has agreed to a post-marketing commitment to study 100 to 2000 subjects for five years to assess malignancies and serious infections.

Other data is derived from post-marketing registries and also from spontaneous post-marketing reports.

Several serious adverse events have been observed with each of three approved TNF blocking agents. This includes serious infections, including tuberculosis, opportunistic infections including histoplasmosis, listeriosis, coccidioidomycosis, and pneumocystis carinii pneumonia, as well as non-opportunistic infections.

All three agents have also been associated with demyelinating events and with autoantibodies and

the development of new autoimmune disease, in particular very uncommon cases of lupus-like syndrome.

For etanercept and infliximab,the safety concerns are most generally based on post-marketing reports. However, some of the concerns have emerged in controlled trials in other diseases than rheumatoid arthritis. However, for adalimumab, a much larger safety database was obtained and available at the time of approval, and you will hear more about this later.

So the same serious adverse events were observed pre-marketing. So we have a much better idea about their incidence for this product. Many of the serious adverse events are consistent with known mechanism of action of these agents. That is an inhibition of an important arm of host defense, for example, infections and possibly lymphoma.

Other serious adverse events are unanticipated -- for example, deleterious effects on patients with congestive heart failure, and also demyelination.

The agency has communicated the risks as they have emerged in a variety of ways. They are

stated in the package insert under the Precautions section, in the Warning section and, where appropriate, as a boxed warning.

The agency has asked the companies to issue "Dear Healthcare Provider" letters. The agency has published peer reviewed scientific publications communicating these safety concerns. We have presentations to the Advisory Committee, including the most recent one in August of 2001, as well as presentations at medical meetings, including several presentations at the American College of Rheumatology annual meeting.

Let me make a couple of points about the package inserts. It has been noted by a number of people that the warning is not identical for each product for the safety concerns that we have talked about. What the FDA has done in deciding on the appropriate language is to look at the data available and, where the data are similar, especially where there is a biologic rationale, class labeling may be warranted. But where the data differ, different language may be appropriate for different agents.

For an example, I would like to talk about tuberculosis, which differs in the infliximab and the etanercept label. For infliximab, tuberculosis was seen in the clinical trials. Cases of tuberculosis, some fatal and some with -- many with unusual presentations, were observed in post-marketing reports.

The reporting rate, based on the post-marketing data, was estimated to be severalfold higher than the incidence in the U.S. population. This asterisk is to remind me that, when we look at post-marketing spontaneous adverse event reports, there is usually a degree of underreporting. So the reporting rate that we saw probably underestimates the actual incidence.

Many of these cases of tuberculosis occurred in patients who were not otherwise considered at risk for tuberculosis.

Based on these data, a boxed warning was put into the REMICADE label, and screening and prophylaxis is recommended for all patients.

With etanercept, uncommon cases of

tuberculosis were seen in the post-marketing experience. The estimate of report -- The reporting rate was similar to the U.S. incidence. However, keep in mind that, due to underreporting, this may be an underestimate.

No cases of tuberculosis were seen in the rheumatoid arthritis trials of etanercept in the U.S. and the European Union, and this involved 3280 patients. Most of the patient reports of tuberculosis with etanercept occurred in patients otherwise considered at high risk. Based on these data, bold warning was put into the etanercept label.

Now why would adverse events differ between the different TNF blocking agents? There are a number of potential explanations. For one, the products have somewhat different mechanisms of action.

Etanercept is a soluble receptor that neutralizes TNF alpha and also lymphotoxin. Monoclonal antibodies work slightly differently. They neutralize TNF but do not neutralize lymphotoxin.

The different products have different affinities for their ligands and different avidities

of binding. They have different ability to lyse TNF bearing monocytes *in vitro* and possibly *in vivo* as well, and the products differ in their immunogenicity.

These differences may contribute to unique efficacy and safety properties of the different agents.

So our agenda today is to update the committee on the known adverse events and on newly documented adverse events with the TNF blocking agents. We will be focusing on tuberculosis, malignancies and lymphomas, liver enzyme elevations and hepatic adverse events, and congestive heart failure. We will also discuss some of the challenges in interpreting open label and post-marketing safety data.

These are the presentations. The next one will be given by Dr. Liang. He will discuss lymphoma and tuberculosis.

CHAIRMAN ABRAMSON: Are there any questions for Dr. Siegel? Thank you, Jeff.

DR. LIANG: Good morning, ladies and gentlemen. Excuse me.

DR. WEISS: Sorry. We have these fancy transition slides that we want to get rid of.

DR. LIANG: Good morning. Sorry for that delay. The outline of my talk will be to update the committee on safety data from clinical trials and post-marketing reports, as Dr. Siegel had mentioned, and also specifically to focus on adalimumab and tuberculosis, followed by the experience of all the TNF blockers with malignancies and lymphoma.

Just as a background slide, in the adalimumab safety database, at the end of the Phase 2 meeting with the agency, FDA had recommended to Abbott to develop a larger safety database because of the serious adverse events that were seen in post-marketing studies with infliximab and etanercept.

to that end, Abbott studied for safety a total of 2070 patients in controlled trials with a mean exposure of seven months, and over 2400 patients in open-label studies with a mean exposure of 24 months.

It is important to keep in mind, however, that the interpretation of open label data is

difficult due to a lack of concurrent control group, though this larger experience and the duration of such trials are beneficial.

In early clinical experience with adalimumab, there were eight cases seen initially in the first 542 patients treat with adalimumab. After discussions with FDA, screening and prophylaxis measures were begun.

In Europe, this consisted of obtaining a chest x-ray prior to beginning the drug, in the United States a screening PPD. For PPD positive patients, prophylaxis anti-TV treatment per CDC guidelines was also recommended.

As a result, there was a reduction but not complete elimination of tuberculosis following these screening and prophylaxis measures. Five cases were subsequently diagnosed in the next 1900 patients treated with adalimumab.

This reduction in TB may have also been contributed due to lower doses used in further studies and enrolling fewer patients from highly endemic areas.

The characteristics of the TB cases include the following: Most reported TB cases from European studies and European sites and were more frequent in patients receiving higher than the licensed dose of 40 milligrams every other week. Most cases were extrapulmonary, and most occurred in the first eight months of therapy in controlled trials.

This may reflect a reactivation of latent infection. As a result, a boxed warning was incorporated into the package insert..

Because of the immunomodulatory properties of TNF blockers, there is obvious concern about malignancies with long term treatment of these products. The assessment of malignancies in relation to these products, however, is difficult, because it is hard to maintain a comparator control arm in long term studies.

On approach would be to compare observed malignancy rates to the expected rate in the general population; for example, using the SEER Database which adjusts for age, gender, race, and geography to calculate standardized incidence ratio or SIR.

With regard to malignancies in the rheumatoid arthritis population, the interpretation of data is even more complicated due to several factors. First off, the lymphoma incidence is reported to be several-fold higher among RA patients, especially those with higher levels of disease activity and inflammation.

The other issue with malignancies in rheumatoid arthritis patients is that most patients that are enrolled in clinical trials already have highly active disease, and most receive concomitant DMARDs with immunosuppressive properties.

This first data table that I will show you represents the malignancies that have been seen with adalimumab in controlled portions of controlled trials.

This distinction is very important, because the controlled portions excludes the patient data that were obtained on the follow-up period, and it is also important because it also gives us a common denominator, if you will, in which to compare other drugs for their treatment times.

In adalimumab treated patients, there were a total of eight malignancies observed out of their controlled trial denominator, if you will, of 1380 patients that were treated for a mean duration of 0.6 years. In the placebo group there were zero malignancies that were seen in controlled clinical trials.

The lymphomas that were observed with adalimumab in controlled portions of controlled trials numbered two. Again, the number of patients was the same.

This table shows the observed versus expected cancer rates for the entire adalimumab clinical development program through August of 2002. A total of 46 malignancies were diagnosed, and the subcategories of lymphomas is highlighted, because the SIRs, Standardized Incidence Ratios, are above 5, and with 95 percent confidence intervals that do not overlap 1.

The 10 lymphoma cases by type according to REAL classification are listed below. As you see, 5 out of 10 or half of the lymphoma cases that were

diagnosed are of the diffuse large B-cell lymphoma type, and the other pathological categories are listed below.

We are going to move on to the experience of etanercept with relation to the malignancies and lymphomas seen in their trials. In controlled portions of clinical trials with etanercept, there were a total of 12 malignancies seen in the etanercept treated patients versus 5 in the placebo treated group.

I have here that one lymphoma was observed in the etanercept treated group. Of these 12 and 5 malignancies, they are represented in this next table and, as you see, we have quite a wide variety of malignancies that were diagnosed in the controlled portion of etanercept trials.

The next slide represents the number of malignancies that -- number of lymphomas that were seen in the entire etanercept clinical trial database. With over 3300 patients representing over 7300 patient years of data with a mean exposure of 2.2 years, six lymphoma cases were reported in all clinical trials,

with an additional 3 cases reported after the follow-up period. The calculated SIR with these data is 2.31, with 2.6 cases expected based on the SEER database.

The next few slides pertain to the experience of infliximab. This slide represents all the malignancies in the controlled portions of controlled trials seen with infliximab. It also includes the ASPIRE data, which is currently blinded data. I just want to mention that, for the ASPIRE data, any malignancy was counted as if it was related to the infliximab arm, giving sort of a worst case scenario, if you will. But it is important to keep in mind that these data are still blinded.

In infliximab treated subjects, there were a total of 22 malignancies for all controlled portions of controlled trials. In the placebo treated subjects, there was one malignancy, giving us a total of 23 malignancies.

The next slide is a listing of all the malignancies seen in the controlled portions of controlled trials, including the ASPIRE data. As you

see, there is also a wide distribution. However, there are three lymphomas that were diagnosed, and the majority of the cases were based on non-melanoma skin cancer.

This next slide looks at the number of lymphomas seen in controlled portions of controlled trials for infliximab. For infliximab treated subjects, there was a total of 3 lymphomas diagnosed, and this is in comparison to zero lymphomas seen in placebo treated subjects. These patients were followed for a mean duration of treatment of approximately a year through all studies.

This slide looks at all of the malignancies seen with infliximab in all clinical trial experience. You see here, for the observed number of cases of malignancies this number is 27. For placebo treated patients, the number is four.

The number of lymphomas in all the clinical trial experience is displayed here. For all studies, there were a total of six lymphomas seen in all the clinical trial experience, and zero in placebo treated subjects.

So our conclusions are that lymphomas have been observed with all three TNF blockers, although these are small numbers with relative short exposure in controlled portions of clinical trials. For the entire database, the calculated SIRs are between two and seven compared to the SEER database. However, a more appropriate comparison would be to the RA population, but accurate incidence rates are not available.

One to three cases of lymphomas have been diagnosed in treated groups for each TNF product, versus zero in the control groups. That gives us a total of the data that I showed of six lymphomas versus zero across all controlled studies.

The biological plausibility of lymphomas associated with these immunomodulatory agents, along with the data presented, raise concern about the causality. Thank you.

CHAIRMAN ABRAMSON: Excuse me. Dr. Liang, I had a question. Maybe others do as well.

In the comment that a more appropriate comparison would be to the RA population, unless I

misunderstood, were not the clinical trials -- obviously, the placebo arms were RA patients, and the rates were still different between the placebo group and the treatment group. Is that true?

DR. LIANG: That is correct. We put that in, because with the subset of RA populations, it is not -- I don't think it is completely agreed upon as to the high -- what the high risk is of malignancies and lymphomas with the RA patients, in particular.

DR. SIEGEL: Could I comment on that also? For the controlled portions of the controlled trials, the appropriate control is there, as you point out, with the RA population using the placebo groups. The problem is with the long term extension studies which makes up the bulk of our experience.

There, to calculate a standardized incidence ratio, you need to use a comparison group, and we don't have accurate numbers on the incidence in the RA population for that part of the data.

DR. WILLIAMS: Can I just clarify something you asked, Steve. That is: When you are looking at etanercept data, is it only the RA data you

are looking at or did you include data from psoriatic arthritis?

DR. LIANG: That data was from just RA.

DR. MANZI: I was wondering if you had any data on spontaneous regression. I'm thinking about some of our methotrexate experience with stopping the drug. In any of these trials, do you know if there has been spontaneous regression with discontinuation of therapy?

DR. WEISS: I'll just briefly comment. There is a population that was included in your handout published -- Two of the authors are sitting right behind me, and I will ask them if they want to make a comment. But they published on a series of approximately 26 cases. Actually Dr. Elaine Jaffe was also involved in reviewing, I believe, some of the slides for those cases.

I believe in one or two of those cases there was spontaneous regression once the TNF therapy was removed.

DR. BLAYNEY: In the studies that you described in those disease conditions, once the

control group finished the controlled treatment, was cross-over to active therapy allowed?

DR. LIANG: It was allowed. However, it was not included in the controlled portions of controlled trial data.

DR. BLAYNEY: But those people, if they did cross over, might pollute the data or add to the safety data, if they developed lymphomas. They would be counted as an adverse event associated with the treatment rather than the placebo in your broad safety data, it sounds like.

DR. LIANG: Well, I think that's the issue here with regard to how to actually count patients that crossed over from placebo to treatment arm. Jeff, do you want to comment on that?

DR. SIEGEL: For the analyses that involved just the controlled portions of the controlled trials, of course, that wouldn't be a concern. But for looking at the drug versus placebo for the total safety databases, that would be a concern.

Generally, patients who crossed over were

not ascribed to the placebo group for that. Their duration of follow-up ended at the point of cross-over. But you are absolutely right, that there was longer follow-up, therefore, for the drug treated patients than the patients in the placebo arm.

CHAIRMAN ABRAMSON: Dr. Krook, do you --

DR. KROOK: It was the same question.

CHAIRMAN ABRAMSON: Okay. Dr. Gibofsky.

DR. GIBOFSKY: Seeing the medians and the means for the cases that you have arrayed, but have we had a chance to look at whether or not there is any segregation as a function either of dosage cumulatively or as a function of onset since time of initiation of therapy?

DR. LIANG: No. That's a good question, but we have not looked at the doses.

DR. SIEGEL: We have done some analyses of the occurrence with -- based on the duration of treatment, in particular with adalimumab, and the data did not indicate an increasing incidence with longer durations of exposure.

DR. GIBOFSKY: And what about for

etanercept?

DR. SIEGEL: I can't recall those data exactly. Perhaps the sponsors later on would have that data.

CHAIRMAN ABRAMSON: Okay, thank you. Thank you, Dr. Liang. The next speaker is Dr. Cote, lymphoma and hepatic toxicity.

DR. COTE: Good morning. Happy Mardi Gras for those of you who are celebrating it later. My name is Tim Cote. I am in CBER.

Today I am going to be talking about lymphomas and liver failure. Most of my time will be spent on lymphomas and with TNF blockers, but this is with a different kind of data, and I want to introduce the data type. It is post-marketing surveillance, also known as the MedWatch program, to somebody who may have submitted reports through it.

This is a system, sort of an open door through which clinicians and others can report adverse events associated with drugs. We call this an epidemiology passive surveillance. We don't actively solicit the reports, but we receive them as clinicians

voluntarily come forward with them to report important events sort of as they function as good citizens in the clinical community.

The greatest benefit of the system is as a means of signal detection. There are some characteristics of those reports that need to be borne in mind before I present the data.

First of all, it is voluntary. There's no laws like we have for other reporting of diseases in public health for clinicians, but it is mandatory that the companies report into the FDA whatever reports clinicians have sent in to the companies.

It is often incomplete, and it is incomplete in two ways. First of all, there may be an unreported number of cases. We can't say with any measure of certainty whether we have 2 percent, 10 percent, 50 percent or 80 percent of the cases which actually occur out in the real world through the system.

It is also incomplete in that the narratives, the descriptions, the clinical descriptions are just volitional reports on the parts

of clinicians. So they may lack important information. They may be sketchy.

When we receive them, they are coded into what we call MedDRA terminology, using a code book. A clerk will go through and, whenever they pick up particular terms, they will assign a code number to it, and it is done with a high degree of sensitivity intentionally so that we may pick up all of those terms that may be in the report.

Causality assessments from these are tenuous by design. We don't have a bar or a requirement of causality in order to receive the reports and includes them in our database and later reviews what we rest upon. I'm going to show you some of that later.

Most importantly, you can't generate incidence rates from this data, because you don't know what proportion of the numerator you actually have got.

Turning now to lymphomas with TNF blockers, there is a rich body of medical literature associating immunodisregulation and lymphoma, and that

is the reason why many of us are here today, because it is biologically plausible that the TNF blockers might cause lymphoma. There's some reasonable reason to expect that that may be the case.

At this point, at this date in our history, we have hundreds of thousands of patients on these drugs, and this increases the public health importance of this committee's consideration.

As has already been mentioned, we have previously published and included in the briefing document a series of 26 lymphomas arising from people who were on TNF blockers, but the causality was explicitly stated in that manuscript as being unclear and subject to further consideration here.

A little bit of more understanding on lymphomas and TNF blockers: As was already mentioned, rheumatoid arthritis and non-Hodgkin's lymphoma are recognized in the medical literature to be associated, and this does complicate the problem of ascribing or not ascribing TNF blockers to have a causal role in the development of lymphomas.

Placebo controlled studies which were

presented earlier have been small, and they have had particularly very small follow-up times relative to the time period that one might expect for a malignancy to develop.

The manufacturer's pre- and post-marketing cohort studies have likewise been short relative to follow-up times that we would expect for carcinogenesis.

We have gone back to the post-marketing data, and this is new information which isn't in your briefing document, because it is only been in the past couple of months that we have been able to generate it out, on lymphomas reported to FDA following TNF blockers from January of 1999 until December of 2002.

There were 863 reports with medDRA terms, both specific terms and nonspecific terms. We cast a wide net, looking for lymphomas and TNF blockers. Four hundred seventy-three of these were on patients who received Infliximab therapy; 390 were patients who had received etanercept therapy and who developed lymphoma.

We went through these and found that, as

we had expected, a large number of them simply didn't have lymphomas, but there were 95 reports of biopsy proven lymphoma diagnosed subsequent to Infliximab therapy, and 63 reports of biopsy proven lymphoma diagnosed subsequent to Etanercept therapy. Together, these represent 158 cases that we have of lymphoma that were subsequent to therapy with one of the TNF blockers.

Over here on this side, 368 did not have lymphomas. Eight had no biopsy. One lacked temporality, and similar numbers for Etanercept cases.

Here's how the cases marched out over time. You can see that, since the licensure of these drugs, there were very few, and they have risen throughout time. We would expect, of course, that the distribution of these drugs has likewise increased throughout this period of time.

A little bit about these patients: most of them had a median -- They had a median age of 64, but a pretty wide range of age, and they were similar between the two drugs. Most of these patients were females.

The indications were slightly different between infliximab and etanercept, as would be expected by the diseases that they are licensed for. Rheumatoid arthritis, however, made up the bulk in both cases. Infliximab also had 21 percent of the cases with lymphoma had Crohn's disease, and there were a higher proportion of other diagnoses associated with Etanercept.

A little bit about the histology of the 158 lymphomas, and this is really a little bit, to underscore how incomplete MedWatch reports can be. Fully half of them had lymphoma. NOS is "Not Otherwise Specified." And 26 of them had non-Hodgkin's lymphoma, not otherwise specified. So this category we can't say very much more about.

Fifteen percent, we knew, were B-cell lymphoma but were not otherwise specified. Hodgkin's disease made up 20 of them, T-cell lymphomas, mantle cell lymphoma, plasmacytoma and one Burkitt's cell lymphoma.

So in conclusion on this topic of lymphomas and what the post-marketing data have to say

about it, they are poorly characterized. It has really not been established if they are the same grade as the general population, because so little has been described about them in the reports. Histologically, they may be consistent with lymphoma secondary to immunodeficiency, but at this point we just don't have the information.

The clinical trials, as Dr. Liang has already described, have found increases in non-Hodgkin's lymphoma risks, but that was based on very few observations. The assessment is complicated by rheumatoid arthritis confounded increases.

The number of cases of lymphoma among persons taking Beta blockers is growing -- excuse me, TNF blockers is growing, and the FDA really needs the input from the AAC to assess the causality and/or propose means to better evaluate the causality.

Okay, moving on here to what I consider the secondary topic of my talk, liver failure. The reason for consideration of it in this talk is that it is a signal for Leflunomide, and thus it is of interest for completeness to look and see what was in

the data on TNF blockers.

In clinical trials also, some patients on Infliximab showed elevated increases in liver enzymes, and I will show you that in just a moment. Here it is. Infliximab mediated ALT increases: If you compare placebo and Infliximab, here are two separate studies, one study of rheumatoid arthritis patients on methotrexate, which is known to increase liver enzymes all in itself, and one study of Crohn's Disease patients without methotrexate.

We can see that there are some fairly modest increases, 29 percent to 37 percent, 36 percent to 42 percent, in ALT. Now you should note that most of these ALT increases were less than two times the upper limit of normal, and there were no clinical sequelae in any of the cases with these ALT increases.

A little bit of the reporting, the cases that were reported through passive surveillance now through the MedWatch program. There were 134 reports to MedWatch citing Etanercept or Infliximab and the MedDRA term that may have coded for liver failure. Then we reviewed those, much as we did the previous

ones.

Fifty of these reports actually had well documented liver failure following an anti-TNF therapy. But when we looked more closely at these 50 reports, we found that fully 43 of the reports had other proximal causes or other possible causes at least for their liver failure, and only seven of them lacked another cause. However, many of those seven were poorly described, and we have asked for further information on them, and we are continuing to evaluate them.

Here are those other causes. Thirteen were associated with sepsis. Again, we can't say that this wasn't an indirect cause of the TNF blockers, because sepsis may well have been associated as an adverse event from the TNF blockers themselves. Eight of them had tuberculosis, in many cases disseminated tuberculosis, and were on INH therapy. So there is another possible cause. Ethanol, Graft-versus-Host disease, viral hepatitis, other drugs which may cause liver failure, and other causes among the remaining ones.

So in conclusion on this topic of liver failure and the TNF blockers, liver failure with TNF blockers appears to be a fairly rare event. while there are a large number of people on TNF blockers, chance occurrence to explain this is pretty unlikely, because the baseline rates are generally thought to be about one per million in the general population for liver failure.

Still, causality can't be ruled out, and some concern remains warranted. That concern is being addressed through further clinical data which is pending on those remaining seven cases. Thank you.

CHAIRMAN ABRAMSON: Thank you. Questions for Dr. Cote? Dr. Gibofsky?

DR. GIBOFSKY: An extension of my previous question to Dr. Liang: If you look at the 158 cases of lymphomas which were aggregated into Crohn's Disease, rheumatoid arthritis and other, if you separate them out by category, do any patterns emerge either in terms of relationship to duration of therapy or onset since therapy was initiated?

DR. COTE: No. No further patterns have

emerged at this point in relation to either of those two questions. In addition, that burden of disease, those 158 cases, were similarly shared between Etanercept and Infliximab.

CHAIRMAN ABRAMSON: Dr. Jaffe?

DR. JAFFE: Do you have any data on EBV positivity, since EBV is often found in the lymphomas associated with rheumatoid arthritis and other immunosuppressive agents?

DR. COTE: It's a very good question. It is a reasonable question to address. We don't have the data. It could be reasonably ascertained by getting the blocks and doing the tests.

CHAIRMAN ABRAMSON: Dr. Blayney.

DR. BLAYNEY: I think there is a great danger to over-interpreting the data that you have. In the MedWatch program, has there ever been any proof or any tests with known adverse event in a well characterized population to try and understand how much of that gets into the MedWatch database in any --

DR. COTE: There have been some studies. There's a number that is bantered about as ten

percent. However, that number is very subject to different influences, one of which is the adverse event of interest. Some adverse events are going to have a higher proportion. Some are going to have a lower proportion.

We know that these 158 are the minimum number of cases which have occurred, but what proportion of the total they may be is unknown.

DR. BLAYNEY: And I think there's -- You know, as these events become known among the users of these drugs, there's a potential for ascertainment bias --

DR. COTE: Absolutely.

DR. BLAYNEY: -- in reporting.

DR. COTE: As things get reported, more reports come in. You are absolutely right.

DR. BRAUN: I'd just like to add to that. My name is Miles Braun from FDA. It is really hard to come up with a rule of thumb about the proportion of reports that would be reported to FDA, and there's been, in particular, work in the vaccine side that shows that it could range from two or three percent up

to around 70 percent, depending on what the adverse event is, and different characteristics of the adverse events, including the time between when the product is given and when the adverse event occurs, and what the degree of recognition of the adverse event is.

So that is -- It's a good question. It's one of the limitations -- one of the multiple limitations of dealing with these data.

CHAIRMAN ABRAMSON: Yes, Dr. Krook.

DR. KROOK: Kind of a follow-up to one of the other questions. In the MedWatch program, any spontaneous remissions as long as you've collected these numbers? I mean, I realize the data is incomplete, but just as you get these, whether that is in those.

DR. COTE: In all honesty, we haven't reviewed the 158 series to know whether or not that is the case. It is something that we will do when we go back and re-review it, and I'd be happy to let you know in follow-up.

CHAIRMAN ABRAMSON: Dr. Jaffe?

DR. JAFFE: As you presented the data,

based on the MedDRA culling about three-quarters of the cases were thrown out as not being lymphoma?

DR. COTE: The main reason is because we used some very nonspecific terms for lymphoma, things like infiltrates and things which were very nonspecific terms, in an effort to make sure that we caught as many of the lymphomas which were in the MedDRA in the database.

So that's the reason why a large number of -- large proportion were thrown out.

CHAIRMAN ABRAMSON: Can I look at your slide 7 and follow up on Dr. Gibofsky's question? The accrual rate of cases with time could either be numbers of exposed or a latency period of duration of exposure.

DR. COTE: Absolutely

CHAIRMAN ABRAMSON: Do you have data on the average time from the onset of treatment to the development of lymphomas?

DR. COTE: We did try to look at that. Unfortunately, the data within the reports wasn't sufficient for us to bring it forward. Probably only

30 percent had the requisite data diagnosis of the lymphoma and date of first treatment with the TNF blocker therapy.

In going back to these patients -- and, of course, that is always an option to us, both at the FDA level or at the manufacturer's level -- that information could be obtained. It's information that we wanted to see, too.

CHAIRMAN ABRAMSON: Other comments? Dr. Krook.

DR. KROOK: Taking the same question that you just asked, and again this is all taking that same graph that you have, can you put that against the use of one of these drugs that at the same time -- I mean, these are cases reported. The amount of drug being used is increasing.

DR. COTE: We can, and probably the manufacturers will show you information on the distribution of drug. It will be very similar. The slope of the curve will be very similar.

DR. KROOK: That's what I thought it would be.

CHAIRMAN ABRAMSON: Okay. Thank you very much. The next speaker is Dr. Unger on congestive heart failure.

DR. UNGER: Good morning, everyone. This will take a second to load. If I could talk and chew gum at the same time, I could maybe introduce myself while I do this and get started, but I'm going to wait.

DR. WEISS: We have an old version of PowerPoint. It's very slow in the government.

DR. UNGER: Again, I'm Ellis Unger. I am a medical reviewer and team leader in the General Medicine Branch in the Office of Therapeutics in CBER, and I am going to talk about anti-TNF alpha strategies in congestive heart failure, and I am going to speak primarily on data form randomized controlled clinical trials in heart failure patients, and I will spend a little bit of time talking about some post-marketing reports for congestive heart failure.

The cardiology community enthusiastically embraced the hypothesis of anti-TNF strategies in congestive heart failure. There were clinical

observations of elevated TNF alpha levels in patients with congestive heart failure, particularly patients with cardiac cachexia.

There were some preclinical data showing TNF alpha induced left ventricular dysfunction and deleterious effects on left ventricular remodeling, and these led to anti-TNF alpha hypotheses that TNF-alpha contributes to the morbidity of congestive heart failure and that anti-TNF-alpha therapies would have salutary effects in patients with congestive heart failure.

On the basis of these hypotheses, a number of clinical trials were initiated, and the ones that I am going to be talking about this morning are two randomized trials with Etanercept and one randomized controlled study with Infliximab.

The etanercept studies went by the acronyms "RENAISSANCE" and "RECOVER." That is how I will refer to them this morning. Because the studies were so similar, they were regarded as sister studies. I will actually present the two of them together.

RENAISSANCE was conducted by Immunex in

North America and enrolled approximately 900 subjects, so a fairly large study. RECOVER was conducted by Wyeth in Europe, Israel, Australia, and New Zealand, and it enrolled 1100 patients.

Both were Phase 2/3 studies, randomized, double blind, placebo controlled, multi-center studies.

For inclusion, patients had to have CHF on an ischemic or non-ischemic basis, an ejection fraction less than 30 percent, symptoms of congestive heart failure for at least three months, and New York Heart Association Functional Classification 2, 3, or 4. Patients also had to be receiving a diuretic and an ACE inhibitor.

Now this is a somewhat complicated slide. So bear with me. RENAISSANCE is shown over here, and RECOVER is shown over here. Both used Enbrel 25 mg SC, and placebo. But the Enbrel was given on different schedules.

So for RENAISSANCE Enbrel was given two times per week or three times per week, two times per week being the recommended dose for rheumatoid

arthritis. For RECOVER, which was the European study, Enbrel was given once a week or twice a week. The treatment duration was 24 weeks.

The clinical endpoints were: First, a clinical composite score, which was assessed at 24 weeks, that I will explain momentarily; and a combined endpoint across both studies of mortality or congestive heart failure hospitalization. For that endpoint, the twice weekly and three times weekly groups were combined, and the once weekly group in the European study was not included.

This clinical composite score was regarded as worse if a subject died, if they were hospitalized for heart failure, if they had worsened New York Heart Association functional classification, or if they global assessment, judged by the subject, was moderately or markedly worse.

The composite score was improved if, first, the clinical composite score was not worse, and New York Heart Association functional classification was improved, or the global assessment was moderately or markedly improved.

The third possibility was unchanged, which was the categorization that the score was neither better nor worse.

Now I'll go into the results of these two studies. First, both studies were stopped in March of 2001. At a planned interim review, the DSMB recommended that both studies be halted, because the pre-specified results indicating futility had been observed.

At that point, because the studies did not initiate enrollment at the same point in time, the median follow-up in RENAISSANCE was 12.7 years, and for RECOVER -- months, excuse me -- and for RECOVER, 5.7 months. So approximately a twofold difference in terms of the data for the two studies.

The baseline characteristics for RENAISSANCE were fairly typical of the congestive heart failure patient population. I point out that approximately one-quarter of the patients were functional class II. Half were functional class IIIa. Another quarter were a functional class IIIb, and a very slim minority were function class IV.

The treatment groups were very well balanced with respect to demographic and baseline characteristics, and I won't show them, but I will point out that there were four notable exceptions, and I point them out because they all tend to favor the placebo group.

So for the placebo group on average, the baseline blood pressure was slightly higher. The six minute walk was slightly longer. Antiarrhythmic use was less frequent, and atrial fib or flutter was less frequent. So the imbalances were small, but all would be associated with a more favorable prognosis in the placebo group. That's why I mention them.

For RECOVER, the European study, again patients were very typical congestive heart failure patients, and the breakdown by New York Heart Association functional classification was quite similar to the North American study.

This is the primary endpoint, week 24, for RENAISSANCE. The results are shown with -- Worse results are shown in blue, improved yellow, and no change is white. The results are most notable for an

increased percentage of patients who were in the "Worse" category for the twice weekly and three times weekly Enbrel compared to placebo.

These are the same data for RECOVER, the European study. In this case, the data were most notable in the twice weekly Enbrel group, a trend toward increased number of patients in the "Improved" category. So there seemed to be a difference.

The other co-primary endpoint was all-cause mortality and congestive heart failure hospitalizations across both studies, again the twice weekly and thrice weekly Enbrel groups. You can see that there is a trend favoring placebo in terms of a worse outcome in patients who received Enbrel.

I will tell you that the difference between the groups was mostly driven by a difference in mortality and not congestive heart failure hospitalizations. So we are going to look more in depth at the mortality.

This is the mortality data for RENAISSANCE. The white line represents the placebo group, yellow twice weekly, and blue thrice weekly

Enbrel. You see the difference here between the groups. The percent mortality was at 14.2 in the placebo arm versus 17.9 in the twice weekly Enbrel and 19.8 in the three times weekly Enbrel group. This was concerning to us.

For RECOVER, you see kind of a different trend. Actually, the placebo patients looked to be worse than the patients on Enbrel. However, because of the difference in length of data, length of follow-up, I will point out that at this point only one-fourth of the patients were still at risk. So, really, the data are quite sparse out here.

Given the differences between the outcomes of the two studies, we looked at some of the difference in the patient populations to try to identify factors that might impart a worse prognosis in patients with heart failure receiving Enbrel, and there were some differences in terms of race, in terms of blood pressure, potassium sparing diuretic use, digitalis and lipid lowering agent use.

I will tell you that none of the exploratory analyses really identified factors that

appeared to put patients at increased risk on Enbrel with heart failure. But there was one subgroup analysis that I would like to go over with you.

Again, this is a *post hoc* subgroup analysis, and it has its limitations, but actually, when I did this analysis, my hypothesis was that patients who have more severe heart failure, functional class IIIb, might be more susceptible and vulnerable to the effects of Enbrel.

In fact, that hypothesis was not borne out. For patients who were more severely affected with heart failure, there appears to be no difference between Enbrel and placebo. And in fact, the difference in the study was driven by the difference in function class II patients.

The conclusion from this is simply that we cannot provide reassurance to physicians that patients with milder forms of heart failure are at lower risk of Enbrel induced deleterious effects.

It is worthwhile to go over some of the SAEs and AEs, basically, to look for clues in terms of the mechanism. One would wonder whether Enbrel had

deleterious effects in terms of rhythm, in terms of ischemia, maybe in terms of hemodynamic factors, maybe negative inotropic effects.

To make a long story short, we don't really find any clues in looking at the adverse event reports that would point us in the direction of one mechanism or another.

The selected AEs are interesting in that we see a trend toward an increased number of a couple of the AEs. Realize, these are selected. Dizziness and chest pain seem to be more frequent in patients who received Enbrel than in placebo patients, but again they are selected.

In terms of SAEs, the main one was increased congestive heart failure, which would be as one would expect.

So for etanercept in congestive heart failure, there is no evidence that Etanercept is beneficial in congestive heart failure. The data suggest harm, though the results are not conclusive.

The key finding of concern was a trend toward higher mortality in Etanercept treated subjects

in RENAISSANCE. This concern was heightened by the apparent dose response relation.

The results of RECOVER do not substantiate the findings of RENAISSANCE with respect to Etanercept induced mortality in congestive heart failure. And the greatest concern was for an Enbrel dose higher than that currently licensed for rheumatoid arthritis in the U.S. This was a three times a week does.

The data do not suggest a specific mechanism of action leading to Etanercept related adverse outcomes in the congestive heart failure patient population. Exploratory analyses failed to identify specific factors associated with increased risk of adverse events.

In particular, patients in RENAISSANCE with milder congestive heart failure did not appear to be at lower risk of adverse outcomes.

So from labeling, there is no basis to provide, first, a measure of reassurance for patients with mild forms of congestive heart failure and, second, a listing of factors that appear to predispose to worsening congestive heart failure.

Now I will move to Infliximab in congestive heart failure. There is one study conducted under the acronym "ATTACH." This was done by Centocor. This was a Phase 2 pilot trial, randomized, double-blind, placebo-controlled, multi-center study.

One hundred fifty subjects were randomized equally to Infliximab 5 mg/kg at 0, 2 and 6 weeks or 10 mg/kg, or placebo on the same schedule.

The inclusion criteria included symptoms of congestive heart failure for three months, New York Heart Association functional class 3 or 4, ejection fraction less than 35 percent, and patients had to be receiving a diuretic and ACE inhibitor.

The primary endpoint was the same, clinical status at 14 weeks improved, worse, or unchanged. Here are the data.

There are approximately 50 subjects per group. Again, the patients who had a worse clinical status are shown in blue, and you can see eight percent in the placebo arm versus ten percent with the 5 mg/kg, 22 percent for 10 mg/kg.

The silver lining was that there appeared to be somewhat more patients who were improved, but that was offset by the patients who were worse. Those are the data at 14 weeks. I should have mentioned, that was a primary endpoint.

Another endpoint, a secondary endpoint, was the clinical status at week 28, and the trend basically continued, 14 percent versus 16 versus 31 percent worse in clinical status at week 28.

The sponsor collected all-cause mortality through one year, and there were four deaths in the placebo group, four deaths in the 5 mg/kg group, and eight deaths in the 10 mg/kg group.

On the basis of the interim data, a Dear Healthcare Professional letter was issued on October 18, 2001, which hopefully you all received. It instructed to look at selected adverse events.

In part because the mortality rate in the placebo arm and the 5 mg/kg arm were the same, one might conclude that, in fact, the 5 mg/kg dose of Infliximab is not deleterious. But the selected AE analysis here doesn't bear that out.

You will notice, for dizziness -- these are symptoms -- Some of them are a little bit soft in terms of indicating heart failure, but I think you will agree, they could point in the direction of heart failure. The incidence of dizziness, 4.2 percent, versus 31.4, versus 20; dyspnea, 12.5, 19.6, 24; angina, obviously, points toward an ischemic mechanism: 2.1 versus 5.9 versus 4.8; and hypotension 5.9 and 8 versus zero.

So it suggested a number of mechanisms, maybe hemodynamic effects, maybe ischemic effects, but the whole thing is tempered by the fact that we have very small numbers. But I think, in all, one might conclude that, in fact, the 5 mg/kg dose is not clean. There seem to be deleterious effects at this dose in patients with congestive heart failure.

So for Infliximab there is no evidence that it is beneficial in patients with congestive heart failure. Although the numbers of subjects treated are small, there is a strong trend suggesting increased mortality in congestive heart failure patients treated with Infliximab.

The data do not show an increase in mortality with the 5 mg/kg dose. However, adverse event data suggest that the 5 mg/kg dose is deleterious. The mechanism underlying this apparent effect is unclear.

When we have these data in hand, it caused us to then query our post-marketing reports in terms of congestive heart failure, and that was done by epidemiology. They found 51 case reports as of February 2002. So it was a year ago. Thirty of these were for Etanercept, 21 for Infliximab, and of the 51 cases 42 reports were for new onset congestive heart failure. Half of these had no identifiable risk factors, and nine were reports of the congestive heart failure exacerbation.

Median age was 64 years. Median time to onset was 3.5 months, and 20 percent of these subjects or patients were less than 50 years old.

For those patients less than 50 years old -- there were ten of them -- six had received Infliximab and four Etanercept. The median ejection fraction was 20 percent. Three had underlying risk factors for

congestive heart failure. Ten had none reported, and after discontinuation of the TNF antagonists and institution of heart failure treatment, three reported complete resolution, six improved, and one died.

I think one has to consider the post-marketing data with the limitations of passive surveillance in mind. But nevertheless, they are interesting.

So in summary, overall the significant overlap between congestive heart failure and rheumatoid arthritis in the general population and, to a lesser extent, in congestive heart failure in Crohn's Disease. Data from the randomized controlled trials in the CHF population raised concerns about the safety of Infliximab and Etanercept.

Post-marketing data raised concern regarding new onset congestive heart failure. Comprehensive analyses of the randomized controlled trial databases of all three TNF blockers may be warranted, and the specific language for labeling is presently under discussion. Thank you very much.

CHAIRMAN ABRAMSON: Thank you. Questions

for Dr. Unger? Dr. Blayney.

DR. BLAYNEY: I understand these agents can cause lymphoma and opportunistic infections which are adverse events in the clinical trials. Did the cardiologists not report them or were they so low that they didn't make your list of selected adverse events or is there some other reason you could help me see why those were absent in your slides?

DR. UNGER: Because basically the orientation of the analysis was congestive heart failure, but the data are there and have been analyzed. I don't have any slides to show you, and I would be reluctant to give you the information off the cuff.

DR. BLAYNEY: Perhaps we could -- Can we shed some light on that issue or maybe later on today?

DR. WEISS: Perhaps, actually, when we get to the discussions in the afternoon, we can pull out some of the information that might help address your questions.

CHAIRMAN ABRAMSON: Dr. Ilowite.

DR. ILOWITE: In the RECOVER trial where

they got weekly doses, the patients -- subjects who got weekly doses, was there any temporal relationship of worsening heart function with the dose, because you would expect the drug would be gone toward the end of the week.

DR. UNGER: The study really wasn't designed to capture that kind of information. You can imagine, if a patient comes once every week or once every three -- I can't remember what the exact schedule was, but they weren't coming in more than once a week. So --

CHAIRMAN ABRAMSON: Your penultimate bullet point there -- I assume you are analyzing the clinical development programs?

DR. UNGER: Yes, we are. We debated whether we should promise that we were doing that, but we are doing it.

DR. SIEGEL: I should mention that we have looked for cases of CHF in the clinical trials for rheumatoid arthritis, and no signal emerged. But we want to go back and look in a more comprehensive way in case there's some signal that is more subtle that

might have been missed.

DR. UNGER: I will tell you that, when I went through the adverse event line listings, I came upon patients who had dyspnea on exertion which was categorized as a pulmonary problem, and peripheral edema which was categorized as a body total or metabolic or whatever.

These were not put together as congestive heart failure, and that is pretty typical. So we are going to put them together and see what kind of signals we come up with.

CHAIRMAN ABRAMSON: Okay, thank you. Norman?

DR. ILOWITE: In the Infliximab trials, was there a temporal relationship between the infusion, during the infusion or shortly after the infusion, and worsening cardiac function? Is that data available?

DR. UNGER: Again, the study wasn't really designed to capture that. Vital signs were looked at, and there were no signals. There were no striking hemodynamic effects from Infliximab or Etanercept.

That was something that was of concern in terms of whether it may have, you know, a direct, immediate hypotensive effect, and that wasn't apparent.

CHAIRMAN ABRAMSON: Dr. Elashoff?

DR. ELASHOFF: For a non-M.D., with respect to the CHF cases in the patients under 50 years old, would it be surprising that so many improved, but would that be what you would expect with cases like this?

DR. UNGER: I think it's pretty much what you would expect. Yes.

DR. WEISS: Don't forget, they also -- I mean they withdrew the drug, and then they also had heart failure medication instituted, and again these are post-marketing reports with the sketchiness that is there. So we don't know if it was just, you know, a mild diuretic and then they felt better or, you know, how extensive exactly that their treatments needed to be.

CHAIRMAN ABRAMSON: Okay. Dr. Makuch?

DR. MAKUCH: You indicated that there was a trend toward increased mortality in the RENAISSANCE

trial, and it was heightened by the apparent dose response relationship. The question I have is what happened to the 1x? I was wondering if the 1x group would have perhaps enhanced your ability to see a dose response rather than just the way that you looked at the study results today.

DR. UNGER: Well, the patients who received 1x did about as well as placebo in the European study. There is somewhat of a danger in combining the data because of the different length of follow-up, because they are different studies.

The sponsors did those analyses. I don't have that. So I'd like to show you that slide right now. Unfortunately, I don't have it. The sponsor may have it.

Basically, when you look at that, you know, with its limitations, I think it just reinforces the dose response, although it is not as apparent as it was if you look at the North American data on its own.

DR. MAKUCH: Thank you.

CHAIRMAN ABRAMSON: Yes, Dr. Anderson?

DR. ANDERSON: I have a question which comes out of Slide 23 which compares the subject populations. In view of the quite large difference between the RENAISSANCE and RECOVER populations in their other medications, in particular, potassium sparing diuretic, I was wondering were there any subanalyses -- exploratory analyses done that took into account the other medications that the patients were on?

DR. UNGER: Yes, absolutely. We looked at patients in the North American study who had received diuretics and not received diuretics, and received potassium sparing diuretics and not, and found no signal there. We were hopeful that we would find something, but we didn't.

CHAIRMAN ABRAMSON: If there are no further questions, we thank the presenters for their very lucid presentations, and we will take a 15-minute break. I'm sorry, Dr. Jaffe?

DR. JAFFE: If I could just back up here, Dr. Cote, I have one question for you before you run off. Of the 158 patients with lymphoma, how many of

those patients were also on methotrexate or other immunosuppressive agents?

DR. COTE: I don't have that information right here. I'm sorry.

CHAIRMAN ABRAMSON: Okay. So we will reconvene at a quarter to eleven. Thank you.

(Whereupon, the foregoing matter went off the record at 10:31 a.m. and went back on the record at 10:51 a.m.)

CHAIRMAN ABRAMSON: We are about to begin the second session this morning, and the first presentation will be from Abbott Laboratories. Dr. Lefkowith will be the presenter. In just a short moment, we will get started, Jim, whenever you would like. Dr. Lefkowith.

DR. LEFKOWITH: Good morning. I am Dr. Lefkowith, and on behalf of Abbott Laboratories, I would like to thank the committee and the agency for this opportunity to present our data on adalimumab, now known by the trade name HUMIRA.

After a brief introduction, I will cede the podium to Dr. Fischkoff, who directed the clinical

program, who can present to you our data on adalimumab. With us also this morning is Dr. Bob Tarone of the International Epidemiology Institute, who will detail some of the information behind the SEER database and provide the calculations for the standardized incidence ratios, for example, so you can understand the analyses better behind malignancy and the lymphoma data specifically.

I will end briefly with some comments regarding our recommendations for your consideration.

With us also this morning are Doctors Paulus and O'Dell, who are made available to the committee as practitioners of the art as well as experts in the field.

Adalimumab (HUMIRA) is an IgG1 kappa human monoclonal antibody derived using phage display technology. It neutralizes specifically human TNF-alpha with high affinity and specificity. It resembles, for the most part, endogenous IgG with a half-life of approximately two weeks.

Currently, HUMIRA or adalimumab is indicated in the treatment of adult RA in patients

with moderate to severe disease who have inadequately responded to prior therapy with DMARDs.

It treats both the signs and symptoms of this disorder and inhibits the progression of structural damage as assessed radiographically. It can be used either alone or in combination with other DMARDs such as methotrexate, and the recommended dose is 40 milligrams every other week.

Contained within the package insert are certain specific warnings regarding serious but, nonetheless, uncommon side effects. IN particular, there is a boxed warning regarding tuberculosis which contains within it guidance to the practitioner regarding the appropriate screening procedures prior to the institution of therapy.

There are also warnings within the package insert regarding serious infections, particularly tuberculosis, demyelinating disorders, malignancies, and specifically lymphomas and, obviously, our presentation will focus largely on this latter subject.

I think it is well to briefly review some

of the sources of variability within the data. IN particular, you will hear a variety of presentations today which use different sources for data to base their calculations for rates on. All data are unique in that we are relying only on controlled trials for our rate calculations for serious adverse events.

Registries represent a less well controlled environment, nonetheless useful, and post-marketing surveillance, obviously, is more qualitative and useful for signaling in terms of safety.

There are also important patient variables, particularly baseline demographics of the patients of interest, age, sex, race, and geography being paramount among those considerations. Moreover, disease severity or duration, as you have heard, are important considerations as well.

I would now like to turn the podium over to Dr. Fischkoff.

DR. FISCHKOFF: Good morning. My name is Steven Fischkoff, and it is a pleasure to have the opportunity to present to you the clinical data from the adalimumab development program.

What I will be presenting today is, first, some information about the structure and scope of the clinical development program, and also the efficacy data that supported the registration of HUMIRA. In addition, consistent with the focus of this meeting, the bulk of the presentation will be on safety issues, particularly a number of issues that have been associated with the class of TNF antagonists, specifically tuberculosis, CNS demyelination, congestive heart failure, and malignancies and malignant lymphoma.

In addition, Abbott is committed to continue to study the safety of HUMIRA in the post-marketing period, and understands the importance of those commitments. I will also go through the structure of the program to look at this in the post-marketing period.

The overall program that was filed with the dossier consisted of approximately 2500 patients treated with adalimumab for approximately 5000 patient years. The data that we will be presenting today has a cutoff of August 31, 2002.

Twenty studies in rheumatoid arthritis were filed with the BLA, of which four are pivotal, and we will go into some more detail in a few moments. Approximately 1400 patients received adalimumab in these clinical trials.

In addition to having a large number of patients available for analysis, the length of follow-up was also long. Approximately 2000 patients had at least one year of follow-up, and the overall median exposure to adalimumab in the studies was two years. IN fact, about 40 patients are now in their sixth continuous year of adalimumab treatment.

Four studies were considered pivotal and are shown here. Two of the studies were conducted in patients taking adalimumab with concomitant methotrexate, one in patients taking adalimumab as monotherapy, and one which I will discuss in a little more detail in a manner that was designed to simulate clinical practice.

The first study, DE009, which is also known in the literature as ARMATA, randomized approximately 300 patients to either placebo or one of

three doses of adalimumab. The primary endpoint for this study was the signs and symptoms of rheumatoid arthritis, with the ACR20 score at six months being the primary endpoint.

The next study, DE019, randomized approximately 600 patients to either placebo or one of two doses and schedules of adalimumab. This study also had a signs and symptoms endpoint at six months, the ACR20, but in addition there were two other endpoints, one relating to disability at one year as measured by the disability index of the HAQ at 12 months, and also the ability to inhibit the radiographic progression as measured by the modified total Sharp Score, again at 12 months. I will show you this data in a few moments.

Study DE011 was the one study of the four studies that was conducted in Europe and was conducted in patients who were not taking concomitant DMARDs. Approximately 500 patients were randomized to either placebo or one of four doses and schedules of adalimumab, and again the primary endpoint was the ACR20 score, signs and symptoms at six months.

As you heard before, at the end of the Phase 2 portion of the program, FDA recommended that we increase the overall size of the program so that approximately 1,000 patients would be available with a year of treatment at the recommended dose and schedule. As a result of this, we added study DE031 which enrolled approximately 600 patients.

This study was designed to simulate clinical practice as best as possible in a clinical trial, because it allowed patients to continue their preexisting DMARDs rather than being washed out. Patients enrolled in the study were taking between 0 and 4 concomitant DMARDs.

In addition, they were allowed to increase a DMARD, to increase a corticosteroid or add a DMARD during the course of the trial and remain on the trial. We felt that this would be best to simulate actual clinical practice.

The study was powered so that we could pick up a one percent adverse event rate with 95 percent confidence at six months in either of the treatment groups.

The average age of the patients was 55 years. This was a late stage patient population with a mean duration of disease of 11 years. We have an ongoing study in early RA, but there is no data to present today from that study.

The mean number of prior DMARDs was three, and the patients also had active disease with a mean tender joint count of 30 out of a possible 68, a mean HAQ of 1.6, consistent with moderate to severe disability, and also a mean CRP of 2.8 with an upper limit of normal of 0.8.

In particular, the one study, DE011, which was the monotherapy study conducted in Europe, enrolled the most advanced and sickest patients with a mean prior DMARD value of 4 and the highest tender joint count, HAQ, and CRP.

I will now show you the signs and symptoms efficacy data that supported the registration. The ACR20 was the primary endpoint and, as can be seen, in all four pivotal studies there's a highly statistically significant improvement in patients receiving adalimumab, including even in study DE011

which enrolled the sickest patients and the most advanced patients. Again, this was also highly statistically significant.

The onset of efficacy was rapid. In study DE009, efficacy was statistically significantly improved as early as one week, and remained statistically significantly improved out to six months.

In study DE019, which went out to a year, the efficacy was again statistically significant all the way out to a year, based on the ACR20 score. In addition, the HAQ score, which is not shown here, was also highly statistically significantly improved compare to placebo out at one year.

Now the ACR20 score is clearly important for regulatory approval, but patients also want to achieve higher degrees of relief, and the ACR50 and the ACR70 score are also indicators of this higher degree of relief.

As can be seen here again, in the studies with concomitant methotrexate, in the study with monotherapy and in the study with the concomitant

DMARDs, there was a highly statistically significant improvement in the ACR50. Again, the ACR70 shows the same pattern with statistically significant improvement compared to placebo in all four studies.

The radiographic progression and the ability to inhibit it was measured in study DE019. In this study, approximately 600 patients were randomized to receive either placebo or adalimumab, and X-rays were taken at baseline, at six months, and at one year.

As can be seen in the patients receiving placebo, there was a continuous and linear progression in the modified total Sharp Score over one year. However, in patients receiving adalimumab there was a statistically significant inhibition in the radiographic progression at both time points.

Looking at the two subscores, joint erosion and joint space narrowing, again there is a linear progression over one year in patients who received placebo, but there is a highly statistically significant improvement or inhibition of progression in patients who receive adalimumab.

Disability is another important feature of rheumatoid arthritis, and we used the HAQ -- the disability index of the HAQ to look at that. At six months in all four of the pivotal trials, again, there is a highly statistically significant improvement compared to placebo, and this improvement exceeds what is recognized in the literature as the minimum clinically important difference of 0.22. In fact, DE009 the improvement in the HAQ was statistically significant at two weeks.

So we summarize about the efficacy of adalimumab, that it reduces the signs and symptoms of rheumatoid arthritis as measured by the ACR20/50/70 score. It also inhibits the progression of structural damage of rheumatoid arthritis as measured by the total Sharp Score and also the subscores, joint erosion and joint space narrowing.

It provides rapid onset and durable relief of rheumatoid arthritis, and also, as measured at six months and at one year, there is an improvement in the disability index of the HAQ.

There are a number of safety issues that

have been associated with the class of TNF antagonists, and these are listed here. First with tuberculosis. Tuberculosis, as has been described earlier, has been seen with TNF antagonists and, certainly, there is preclinical data suggesting that in a number of animal models there is decrease in host resistance to tuberculosis that can be seen.

In some cases, there is a higher than expected number of patients who present with either a miliary pattern on chest X-ray or extrathoracic presentation. It is possible that the true incidence may be underestimated by post-marketing reports for the reasons that were cited earlier and, as we will show you in a bit, geographic and patient demographics can also greatly influence the incidence of tuberculosis that could be seen.

As a result of all this, clinicians are being alerted to the possibility of tuberculosis in patients receiving this class of drugs, and certainly, screening for tuberculosis has been recommended and has become standard practice.

In the adalimumab clinical program, there

were 13 cases that were seen in patients who received adalimumab. They were not distributed geographically evenly. Six were in Germany, one in each of four other European countries, two in the United States, and one in Canada.

In addition, there were three cases of tuberculosis in patients who were not on adalimumab therapy, one in a patient receiving placebo, and two in patients who had been off adalimumab therapy, but we had long term reports from their physicians. Two of these cases were in Germany, and one of them was in Italy. This may represent a background incidence of tuberculosis in this population.

The peak incidence of tuberculosis was between three and eight months of treatment, although there were infrequent cases out after a year. All of the patients presented today have recovered with standard anti-tuberculous therapy, and there were no deaths.

We looked again at the impact of screening, first within the pivotal trial program and its follow-up and then in the open-label extension. I

have shown before in the early studies, Phase 1 and 2, screening was not yet implemented, and we had eight cases of tuberculosis.

Later in the Phase 3 program, we instituted screening with either our European study, exclusion from the study if the chest X-ray was positive, or in the United States and Canadian studies a recommendation but not an insistence on prophylaxis if the PPD was positive.

In the larger number of patients, there was only one case of active tuberculosis, and this particular case was a patient who was PPD and chest X-ray negative at baseline, but on presentation of active disease was positive for both, suggesting that this is a primary case of tuberculosis.

Dr. Liang referred to five cases of tuberculosis after the institution of screening. This is one, and there were four additional cases that were seen in the open-label extensions. Two of these cases had evidence of latent tuberculosis infection at baseline but, for one reason or another, one because of a change in the recommendations, and one because

the investigator chose not to, these patients were not screened, and potentially could have been prevented.

I will move on to CNS demyelination. In the adalimumab clinical program, there were four cases that were seen. One of them presented as optic neuritis. Three of them presented with paresthesias. Of these three cases, one of the patients had a prior diagnosis of probable multiple sclerosis in the past.

All of these cases resolved. The optic neuritis case resolved on high dose corticosteroids. One of the paresthesia cases resolved partially with Copaxone, and two resolved completely spontaneously.

Congestive heart failure was a subject of discussion this morning. Abbott has not done specific trials in patients with congestive heart failure, nor does it intend to. But as suggested before, we have looked into our RA patient database to see what signals there might be.

In the pivotal studies there were seven patients with a prior diagnosis of congestive heart failure who were enrolled and received placebo, and 18 patients who were enrolled and received adalimumab.

None of these patients suffered a relapse during the pivotal portion of the studies.

In addition, there were patients who did not have a prior diagnosis of congestive heart failure, but as can be seen, the number of patients who developed new onset heart failure appears to be balanced between active and placebo.

I will now move on to malignancies and malignant lymphoma.

Based on the literature, the impact of TNF antagonism on the risk of developing a malignancy is unclear, because there are some studies that suggest that the risk could be increased, and some studies that suggest that the risk could be decreased.

Specifically, TNF is involved in the immune surveillance for cancer in the body, and it is also known that supraphysiologic -- in other words, pharmacologic -- doses of tumor necrosis factor can induce regression of established tumors.

On the other hand, there are also studies showing that TNF deficient mice are resistant to skin carcinogenesis, and TNF is also a growth factor for a

number of human lymphoma and leukemia cell lines.

To look at the potential impact of adalimumab on cancer risk, we used the 1992-1999 SEER database, and we used a matched patient population, matching for age, sex, and race. Based on this, we would expect to see 45.5 cancers in the treatment period, and 46 were observed.

Therefore, the standardized incidence ratio, meaning the ratio of the number of cases observed to the number of cases expected, was one with a confidence interval of 0.7 to 1.3.

We looked to see if there were any particular types of tumors that had an increased incidence based on their SIRs, including lymphomas and common types such as those shown here. As can be seen, with the exception of malignant lymphoma which had a confidence interval that excluded one, the other types did not show any signal of a potential increase in the incidence of those cancers.

We also looked over time, and with up to five and a half years of follow-up it appears that the risk of developing a cancer is constant over time, and

there is no evidence of either early onset of cancers or any acceleration in the rate of developing a malignancy.

Malignant lymphoma is different, because as we have heard this morning, there have been multiple reports in the literature that the incidence in patients with rheumatoid arthritis is elevated. And as can be seen, there are a number of large patient based studies. There are some case controlled studies as well and, as can be seen here, the standardized incidence ratio or the odds ratio from these studies varies somewhere between 2 and 8.

One study that tried to pick this apart was the study of Baecklund *et al.* that looked at the odds ratio as a function of level of disease activity. Baecklund found that there was a fairly strong correlation with higher levels of disease activity being consistent with markedly elevated incidence of malignant lymphoma.

If you use the criteria that Baecklund *et al.* used to assess patients, what they did was they took a measure based on erythrocyte sedimentation

rate, giving patients from 1 to 3 points, the number of swollen and tender joints, adding an additional 1 to 3 points, and the physician's global assessment of disease activity, again 1 to 3 points. So that a score would be somewhere 3 and 9.

the mean of these scores from the visits was taken, and then this chart was used to assign patients to low, medium or high disease activity, and that was the score that was shown on the previous slide. Based on this classification, the majority of patients in the adalimumab program would be medium to high.

There were nine cases of non-Hodgkin's lymphoma and one case of Hodgkin's disease, for a total of ten, that were seen in the adalimumab clinical development program. Calculating the standardized incidence ratio, it was 5.5, which is consistent with the odds ratio of 5.4 that has been seen for patients with moderate -- with medium levels of activity of their disease.

One of the questions that the committee has been asked is to discuss the tumor types, the cell

types. So we have broken this down, first by the cell type here, and we have compared two studies from the literature that looked at the distribution of tumors, lymphomas, that were seen in patients with rheumatoid arthritis.

In our program 80 percent of the tumors were B Cell type, one was T Cell type, and one was Hodgkin's. This is certainly consistent with the prevalence of B Cell lymphomas that's seen in these patients.

Looking at the histology and comparing it to the rates that were described in the same two publications, as you can see, the rates of each of the different histologic types again matches very well with what was expected in the literature from patients who have rheumatoid arthritis.

This is the detailed breakdown of the patient characteristics. What I would like to point out is that in these patients the mean age was 63, which is greater than the overall mean age of the population of 55, and the mean number of years of RA was 12 1/2, greater than the mean duration of RA of 11

that was seen in the overall population, consistent with age and duration of RA being risk factors for the development of malignant lymphoma.

Looking again to see if there was any influence of time on the risk of developing lymphoma, in this Kaplan-Meier analysis, again, we see no early onset of malignant lymphomas, and we see no accumulation or consistent with cumulative toxicity.

So regarding safety, we conclude that TNF antagonists, including adalimumab, have been associated with cases of active tuberculosis. Screening appears effective at reducing the incidence of active tuberculosis and has become standard of care.

Rare cases of CNS demyelination have been observed, and the malignancy rate that we saw in the adalimumab clinical program is consistent with a matched, based on age, sex and race, general population.

In addition, the lymphoma rate is higher than the general population, but is consistent with an RA patient population matched for disease activity.

Abbott is committed to continuing to study the safety of adalimumab in the post-marketing period and has committed to the following programs:

Number one: Abbott is committed to continue long term safety trials, which currently consist of approximately 1700 patients, for a total of five years. These will be done under completely monitored conditions. This will increase the overall size of the safety database by a factor of two but, more importantly, will increase by a factor of greater than 10 the number of patients that have been followed for up to five years.

This will enable us to precisely calculate incident rates of adverse events of interest, because we will be fully capturing all events and fully monitoring all patients.

We will supplement this with the European registry, which will enroll approximately 3000-5000 patients, some of them coming from expanded access programs. This will provide a large supplemental experience with which we may hope to detect new rare adverse events.

Abbott is either conducting or will shortly conduct studies in some additional indications, as shown here. We are conducting studies in juvenile rheumatoid arthritis and early rheumatoid arthritis. Studies are ongoing in Crohn's disease and will shortly start in psoriasis, psoriatic arthritis and ankylosing spondylitis.

In addition, despite the limitations discussed before about spontaneously reported adverse events, Abbott will still continue to collect them, and this may allow us to detect potential new rare signals or perhaps changes in pattern that are consistent with changes in medical practice.

Our overall assessment of the risks and benefits of adalimumab is as follows. Adalimumab is effective in reducing the signs and symptoms of rheumatoid arthritis and inhibiting the progression of joint destruction.

TNF antagonists have been associated with rare cases of tuberculosis and CNS demyelination, and guidance is provided to both the patient and the practitioner in the various package inserts.

Adalimumab does not appear to contribute to the increased risk of cancer of malignant lymphoma, based on the information that I have shown before, in the RA patient population; and the benefit risk assessment is, therefore, quite high in favor of adalimumab, and Abbott believes that this represents a significant contribution to the care of RA patients.

I will now turn the floor over to Dr. Robert Tarone who will go through in some detail the methodology that is used for calculating the standardized incidence ratios.

DR. TARONE: I want to briefly describe the calculation of standardized incidence ratios or SIRs, and comment on their use in evaluating cancer in clinical trials.

The standardized incidence ratio is an estimate of the relative risk of cancer in a defined cohort followed for a specified period of time. Relative means relative to the cancer risk in the general population from which the cohort was derived.

Now the SIR is often represented as 0 divided by e, and that reflects how it is calculated.

The SIR is the observed number of cancers in the cohort divided by the number of cancers that would be expected if the cohort members have the same cancer risk as the general population.

Now to compute this expected number of cancers, we obviously need to have good estimates of age-specific cancer rates for the general population, and for the adalimumab trials we used the SEER database, the National Cancer Institute SEER program.

This data comes from population-based cancer registries. What that means is that SEER tries to ascertain every single primary cancer diagnosed in the catchment area of the SEER registries, and these catchment areas are defined by county or state lines.

This is important, because that means that SEER can get form the Census Bureau very accurate estimates of the population size at risk by county and state for the different age groups, which allows them to have the denominators needed to calculate the age-specific cancer rates.

Now SEER does not collect data on basal cell or squamous cell skin cancers, and it does not

collect data on metastases, primary cancers only.

There are currently 11 SEER registries, and there have been since 1992, and they cover approximately 14 percent of the U.S. population. Now just for the record, very shortly there is going to be an expansion of SEER for future applications. 2003 may be a slight optimistic. Actually, next month SEER will report the incidence data for the year 2000. It is delayed somewhat, because they have had to make adjustments to the denominators based on the 2000 Census.

So probably in early 2004, the 2001 incidence data will be reported, and that will be based on four additional cancer registries. After that, SEER will cover 26 percent of the U.S. population, and these registries were added with minorities in mind. In fact, there will be 24 percent coverage of African Americans, 44 percent of Hispanics in the United States, and 59 percent of Asian Americans.

For our current purposes, all we really need to know -- What is important is that we can get

sex-specific, race-specific, age-specific cancer incidence rates from SEER in five-year age intervals through 80-84 years of age.

We use the rates from the 11 registries, 1992-1999. 1999 is the most recent data available. So how do we use this to calculate the expected value? Well, take each year or fraction thereof that a person in the trial taking adalimumab is followed at a given year of age for diagnosis of cancer. Call that y.

Let r be the annual incidence rate of cancer at that age in the general population for a person of the same race and same sex. Then the contribution to the expected number of cancers for that year of age and that person is y x r. You get a similar contribution for every year of age that that patient is followed. Sum those up to get the contribution for that person.

This is best illustrated by an example. So let's consider a white man with first adalimumab injection at age 79 years, 3 months, who is then followed for 2.5 years. Okay. So that's three-

quarters of a year that he is followed at age 79.

We get the lymphoma rate for 75 to 79 years of age from SEER for white men. Multiply that by 0.75, the length of time he was followed at age 79, and this is his contribution at age 79.

Now he was also followed for an entire year age 80 and three-quarters of a year at age 81. So we get the SEER rate again for white men in the age group 80-84 years of age. Multiply that by the length of time he is followed in that age category, and here you have the contribution of this man to the overall expected value from ages 80 and 81, and his total contribution then to the expected number of lymphomas in all of the patients is the contribution at age 79 plus the contribution at ages 80 and 81. It is 319 per 100,000 or 0.0032. This is his contribution to the total expected value.

What this represents is the probability that he would have developed a lymphoma in the 2.5 years he was followed using SEER rates for white men.

Now you get a similar contribution for each of the 2,468 patients who received adalimumab,

and the overall expected value is just the sum of all these 2,468 expected contributions. Then the SIR is calculated by dividing the observed number of lymphomas to this overall expected number of lymphomas.

This is the result. You have seen this before. For lymphoma there were 10 observed lymphomas. The total expected was 1.8. Divide 10 by 1.8, and you get the SIR of 5.5.

Now I think it is noteworthy that both NHL and Hodgkin's disease were elevated, even though this is based on small numbers. This was actually seen for all three of the drugs under consideration today. There is an increase in both NHL and Hodgkin's disease, and this is exactly what you would expect form a rheumatoid arthritis population.

All of the large population based cohort studies have shown that both NHL and Hodgkin's disease are at increased risk in rheumatoid arthritis patients. In fact, most have shown a slightly larger relative risk for Hodgkin's disease than for NHL.

All right. The committee has been asked

to make recommendations -- Well, I want to say one more thing about that, because that contrasts with what is seen in severely immunosuppressed patients, the implant patients.

In those patients, only NHL is elevated. There is no evidence that Hodgkin's disease is elevated by severe immunosuppression.

All right. The committee has been asked to make recommendations about the use of SIRs to evaluate cancer risks in clinical trials and also with regard to labeling. So I have just a few cautionary comments.

The calculation of an SIR assumes that the cancer risk in the cancer registry population is the same as the cancer risk in the cohort that you are following. This is -- Well, this is never strictly true for any application in epidemiology of SIRs, and that is true also of clinical trials, and for at least two reasons in the adalimumab trials, and in general, one related to geography and one related to calendar period.

Sixty-two percent of the patients in the

adalimumab trials were from the United States or Canada. Now, obviously, there is no problem in using SEER for them. Canada has very similar lymphoma rates as the United States.

The other 32 percent were from Western Europe, several countries, and from Australia. Now there are no good, large cancer registries in those countries in Europe or in Australia. So we used the SEER rates for all of the people, including those from Europe and Australia.

What can be said, if you go to the World Health Organization, either their website or their CD-ROM, and look at a map, they have global maps now for incidence and mortality for lymphoma, and all of the countries represented in the adalimumab trials were in the highest category of lymphoma risk.

So it is probably not too unreasonable to use SEER for all of the patients in these trials, but it is an assumption.

The second issue has to do with calendar period, and this is always going to be an issue in using SIRs in these clinical trials, because the

clinical trial follow-up is very recent years, and there is always a delay in these cancer registries when you can actually analyze the data.

We used the data up through 1999 to analyze these trials. Most of the follow-up was after 1999. Now this is unlikely to be a serious problem, because it is very rare to see sharp increases or decreases in cancer incidence in a two or three-year period, and that is generally what the lag is between when these registries report their data.

A second cautionary note is that the follow-up, obviously, in the clinical trials has to be at least to the standard of the cancer registry, and for SEER that is 98 percent. So if the follow-up in the trials has less than 98 percent ascertainment of cancers, then you are going to get an underestimate of the risk in the trials.

A third point: Even if you have totally appropriate registry and you have complete ascertainment of cancer, there is still going to be some bias in these SIRs. That is because cancers in the general population are diagnosed as a result of

usual medical practice in the community, and the patients in the clinical trials get much more medical surveillance.

So it is virtually certain that in some of these patients you are diagnosing cancers during the clinical trial period that, if they had not been in the trial, would not have been diagnosed until after the follow-up period ends.

So there's telescoping of a few cases from beyond the end of the follow-up into the trial period is going to lead to an increase in the SIRs, but I don't think this is so serious as to invalidate the use of SIRs for this purpose. It does argue strongly, I think, to exclude *in situ* cancers from such considerations.

The last point relates to labeling. I think the most serious issue with regard to the use of SIRs in labeling has to do with how you convey the uncertainty in the SIRs. For example, all three of the drugs under consideration had elevated SIRs from lymphoma. They had wide confidence intervals.

There is clearly no significant difference

between the SIRs. So how do you convey the information of these SIRs in the labeling? My personal opinion is confidence intervals are not the way to go.

Most statisticians can't explain confidence intervals. So I don't know what a physician or a patient is going to do with a confidence interval, but this is a question that has to be answered, I think, and it is more serious in the current situation because of the inherently increased risk of lymphoma in these patients.

The differences you see in SIRs may simply reflect differences in the severity of rheumatoid arthritis in the patients that were included in the different trials.

CHAIRMAN ABRAMSON: We have a few moments for -- Yes, of course. Sorry.

DR. LEFKOWITH: I'll be quite brief. I think we would like to propose some labeling considerations for you to contemplate during your deliberations.

I think it is particularly appropriate to

review this example with another therapeutic class of drugs where a rate for serious adverse event was estimated either at 0.02 or 0.04 events per hundred patient years from post-marketing surveillance, but 100 times that rate was derived from clinical trials.

The question is rhetoric. In a way, you are in fact processing or measuring exactly the same event. What differs here is the context, and context is important. So to summarize very briefly, we would like to highlight -- we would like to propose these labeling recommendations.

We believe that information on prevention and screening should be highlighted, because regardless how infrequent a serious event is, if a physician can do something preemptively to screen those patients and to prevent that from occurring, that is serving the physician community as well as patients.

We believe that information on vigilance should be harmonized, because vigilance is important in terms of informing the practitioner to intervene on a timely basis. This will prevent morbidity and

mortality.

Again rates should be described with appropriate context. Patient characteristics need to be described. The nature of the study is important, and I think it is appropriate to add a caveat regarding the limitations on comparability.

SIRs are useful for describing cancer risks with the caveats that Dr. Tarone added, provided that you use an appropriate normative database and an appropriate study vehicle for deriving the number of observed cancers.

Finally, we would offer this last consideration for you to contemplate, whether absolute risk may be more appropriate than relative risk, because these are, in essence, relatively rare serious adverse events, and relativeness may overestimate the probability and lead physicians and patients into drawing the wrong conclusions.

Thank you very much for that last comment. We would be willing to entertain questions of clarification.

CHAIRMAN ABRAMSON: Tom and perhaps the

other speakers can come to the podium. Questions from the panel? Dr. Jaffe.

DR. JAFFE: It seems that the increased incidence in TB but not other opportunistic infections must be telling us something about the effect of the drug on the immune system and perhaps suggest that macrophage function may be targeted more directly than T Cell or B Cell function.

What studies have been done of *in vitro* immune function in these patients or *in vivo* immunologic testing to try to determine the effect of the drug on immunity?

DR. FISCHKOFF: If I understand your question correctly, you are first asking, one, if there is a true difference in not seeing other opportunistic infections and, number two, what tests have been done in terms of looking at that.

Let me start with the second question first. What this slide is showing is a portion of some of the studies that we have done using flow cytometric techniques, which was a substudy of the DE009 study, specifically the United States study in

patients receiving concomitant methotrexate.

What is shown here is that, looking at CD-56 and K-cells and also CD-14 cells, there doesn't appear to be any dropoff or depletion in either of these cell populations, and the end time point is six months.

Regarding the other point, there were, and are described in the label, a number of other opportunistic infections. So that, in fact, we have seen a number of other infections. Specifically, we have seen two cases of aspergillus, one of nocardia, and three of histoplasma.

So, in fact, it is something that physicians do need to be alert to as well.

DR. JAFFE: But not viral infections? I mean, what component of the immune system do you think is being affected? Even though there is not a decrease in macrophages, is there an effect on macrophage function or macrophage chilling?

DR. FISCHKOFF: I would hate to go beyond what it is that we have actually studied. In that one substudy, there were a number of other cell sets that

were looked at and also some functional studies, including some functional studies regarding neutrophils, but that is the limit to which we have studied, and I would hate to speculate beyond what we have done.

CHAIRMAN ABRAMSON: Dr. Blayney?

DR. BLAYNEY: A couple of things, both in your slide and Dr. Liang's slide also. There were no lung cancers seen. Could you comment on that?

DR. FISCHKOFF: Your question is?

DR. BLAYNEY: Does your drug protect against lung cancer?

DR. FISCHKOFF: Well, you know, we did have one case of lung cancer, and we did request that we get an indication, but they asked us to do another study.

DR. BLAYNEY: Also lymphoma is increasing in the general population. Furthermore, in the other iatrogenic immune suppression settings of transplantation and also in HIV immune suppression, one sees lymphoma, but one also sees Kaposi's sarcoma and melanoma, to some extent, in the transplant

iatrogenic immune suppression.

You didn't see that here. Could you comment on that?

DR. FISCHKOFF: Well, let me show you first the data that we have on melanoma. Can I have the original slide that had the rates of the various cancers, the one we just saw?

As you can see, we did have three melanomas. The confidence interval includes one, although any conclusions are being driven here by a very small number of cases. There were no cases of Kaposi's sarcoma.

DR. BLAYNEY: Thank you.

CHAIRMAN ABRAMSON: Dr. Elashoff.

DR. ELASHOFF: Yes. This question is for Dr. Tarone. How stable are these estimate of annual incidence rates when you have broken down by age, sex, race and geographic region? And also do the confidence intervals that you create for the estimated SIRs reflect what is known about variability for those rates?

DR. TARONE: The answer to the second

question is no. They are the usual confidence intervals calculated using exact Poisson methods, and all of the standard methods assume that the underlying incidence rates are essentially parameters that are known.

With regard to the first question, well, even for our blacks and Asians, we accumulated all of the data from 1992 to 1999. So they are likely to be very stable, even for five-year age groups. You mentioned geography. Obviously, we can't -- That was one of the problems. I mean, we had to use the entire SEER database. We didn't try to stratify it by the state of location of the patient in the trial. It was just using nationwide rates.

CHAIRMAN ABRAMSON: I have one final question for this round. Dr. Gibofsky.

DR. GIBOFSKY: Steve, is there any correlation between either the finding of immunogenicity to adalimumab and the occurrence of infection or malignancy, particularly lymphoma? Is there any greater or lesser incidence in the population to develop antibodies than those who do

not?

DR. FISCHKOFF: So your question was, was there a correlation with any important safety parameter and the incidence of immunogenicity?

DR. GIBOFSKY: Right, with particular reference to either infection, malignancy or lymphoma.

DR. FISCHKOFF: This is data from study DE011, which is the study where patients were receiving adalimumab as monotherapy, and overall there were 12 percent of patients that had detectable at some point along the way, and they had multiple -- they had multiple looks to see if there was an antibody.

As can be seen with respect to adverse events, fatal adverse events, serious adverse events, withdrawals or at least possibly drug related adverse events, there is no difference between the patients who have an antibody at some point in their course or those who never have one at any point in their course.

CHAIRMAN ABRAMSON: Thank you. We will have time for questions when we come back in the

afternoon discussion. Thank you very much.

We will move on now to the Amgen presentation, Dr. Burge.

DR. BURGE: Good morning, members of the committee, the FDA, ladies and gentlemen. It's a pleasure to be here today to provide a safety review of etanercept which, as all of you are aware, has become well established as a significant therapy for patients with rheumatoid arthritis, juvenile rheumatoid arthritis, and now psoriatic arthritis.

The efficacy and safety of etanercept has been reviewed before this committee on a number of occasions: The initial review associated with licensure in 1998, the review associated with label extension in 2000, and then the TNF safety review in 2001.

We welcome this opportunity to engage the committee today, and have been asked by the FDA to focus our attention on safety observations relevant to lymphoma and heart failure. We will begin by describing some of the unique characteristics of etanercept, aspects of the etanercept

pharmacovigilance program. We will then share some general observations from the extensive experience accrued with etanercept.

We have asked Dr. Alan Silman to then provide some perspective on the epidemiology of lymphoma in rheumatoid arthritis patients, and we will then review our data regarding lymphoma and heart failure and conclude by reviewing our ongoing pharmacovigilance program.

Recognize that etanercept was originally cloned and engineered by Immunex in 1990, and Immunex was acquired by Amgen in 2002. To avoid confusion, I will refer to Immunex and Amgen collectively as Amgen for the remainder of the presentation.

Several consultants have kindly consented to join us today: Dr. Jeffrey Borer from Cornell University Medical Center; Dr. Mary Crow from the Hospital for Special Surgery in New York; Dr. Annette Langer-Gould from Stanford University; Dr. Alan Silman from the University of Manchester in the United Kingdom; and Dr. Julie Vose from the University of Nebraska Medical Center.

Though etanercept is in the TNF antagonist class, it is distinct as the only soluble TNF receptor utilizing receptor binding specificity. The human protein has low immunogenicity, and no neutralizing anti-etanercept antibodies have been detected.

Etanercept does not active compliment nor does it initiate compliment mediated cell lysis. The dosing schedule and pharmacokinetic profile of etanercept results in a relatively smooth concentration curve throughout the treatment period.

As etanercept may be administered alone or in combination with methotrexate, it is important to note that coadministration with methotrexate does not modify etanercept pharmacokinetics.

We believe that these product-specific differences in structure, function and pharmacokinetics are relevant to etanercept's efficacy and safety profiles. Although the focus of today's discussion is on safety issues, in order to appropriately assess etanercept's benefit risk profile, it is important to appreciate the efficacy of etanercept.

The clinical improvement is rapid, substantial and sustained for up to six years in clinical trials, and frequently permits tapering or discontinuation of concomitant corticosteroids and methotrexate, each of which can be independently associated with safety issues.

In multiple clinical settings,including early rheumatoid arthritis, patients with more advanced disease, patients treated with Enbrel as monotherapy, or in combination with methotrexate, patients receiving etanercept consistently receive ACR20 responses in the 70 percent range. This level of benefit has also been observed in patients with JRA and psoriatic arthritis.

The P-75 TNF receptor was cloned in 1990. Etanercept was first developed and administered to RA patients in 1993. It was initially approved for commercialization in 1998 for the reduction of signs and symptoms of rheumatoid arthritis as used as monotherapy or in combination with methotrexate.

In 1999 etanercept was additionally approved for the treatment of children with juvenile

rheumatoid arthritis, and in June of 2000 Enbrel was approved as a first line disease modifying therapy for rheumatoid arthritis and for an inhibition of radiographic progression.

In August of 2001 we provided a review of etanercept to this committee, and then in 2002 etanercept became the first disease modifying therapeutic approved for the treatment of psoriatic arthritis.

We have long been committed to providing meaningful information regarding the safety of etanercept to patients and prescribers. Even prior to product approval, Amgen and Wyeth jointly made a substantial commitment to the development of a comprehensive pharmacovigilance program.

During the four years since product approval, this program has been further expanded and includes multiple elements, as outlined here. Multiple long-term, open-label clinical trials remain ongoing in North America and in Europe with over 1600 patients entered, some of whom have now been observed for over six years.

Studies of patients with comorbidities, patients on combination therapies have also been initiated to further explore the safety profile of etanercept. Observational studies have been initiated in other special populations, such as children with juvenile rheumatoid arthritis.

The RADIUS program is now nearing its goal of enrolling 10,000 RA patients. This five-year program will permit monitoring of the interaction between therapies, comorbidities, clinical status, and safety. Several national registries of also been implemented in Germany, Sweden, and the United Kingdom.

As the background epidemiology for adverse events in patients with rheumatic diseases is often not well characterized, we have sponsored several epidemiologic studies, including a project with Ingenix UnitedHealthcare, a database with approximately 50,000 rheumatic disease patients to establish the background rates of adverse events in the RA, psoriatic arthritis, and ankylosing spondylitis populations.

Surveillance of adverse events has also been ongoing since product approval in November 1998. Special programs have been in place, such as the Enliven and Enrollment programs. Enliven is a patient support system, and the Enrollment program was in place to help facilitate drug distribution during the previous period of limited supply.

Over 1.2 million phone contacts with the 150,000 patients who have received etanercept therapy have facilitated adverse event reporting. Eighty-eight percent of all reports have been initiated by patients, and follow-up of these patient reports with health care providers accounts for over half of the health care provider reports. We believe that the increased interactions with patients improves safety surveillance.

At the time of initial approval, etanercept filled a significant unmet medical need for patients with RA. Recognizing that the experience at the time of approval was limited, we initiated a significant number of additional clinical programs, some of which serve to satisfy post-approval

commitments.

In August 2001 we met again with this committee and had the opportunity to present a safety update which reflected the greatly expanded experience with that representative over 111,000 patients. We are able to present here today our experience based on over 8,000 patient years of clinical trial experience in rheumatoid arthritis and psoriatic arthritis and over 230,000 patient years of practice experience.

This includes over 1,000 patients in their fifth year of therapy and over 390 patients in their sixth year of therapy.

Serious adverse events, as defined by ICH, are carefully reported and evaluated. As you can see in this slide, whether in early RA or more advanced disease, the rates of serious adverse events are similar between control populations and etanercept treated patients. Furthermore, when we observe over time, the rate of serious adverse events does not increase.

Serious infections, defined as those associated with hospitalization or IV antibiotics,

have also been carefully monitored in clinical trials. Again, the rates of serious infection in the control groups are similar to that seen in the etanercept group in early disease or in more advanced disease. Again, the rates do not increase with prolonged therapy with up to six years.

I would like to focus our attention on a general overview of malignancies before discussing lymphoma in detail.

When evaluating the incidence of malignancies in the clinical experience, we also have utilized the national Cancer Institute database, called Surveillance, Epidemiology, and End Results or SEER database.

This database collects population based information from multiple regions representing 14 percent of the United States population, and provides data regarding incidence, prevalence and mortality of various malignancies.

Utilizing age, gender, and race-specific rates for the SEER database, one can calculate the expected number of cases in the general population

relative to the trial cohort. The expected rate can then be used as a denominator in calculating the standardized incidence ratio or SIR.

This table represents data regarding malignancies observed in etanercept clinical trials. One can see that the control group had five malignancies observed with 3.57 expected and an SIR of 1.40. In the etanercept group there were 11 with 8.80 expected with an SIR of 1.25. In the entire etanercept experience, we see that there were 55 observed, 56.2 expected, and an SIR of 0.98.

The rate of malignancies shown on this slide is a rate or events per 100 patient-years of observation. Once again, the rate is similar between the control and the etanercept groups, and there is no increase over time.

Now we would like to have a brief discussion about the epidemiology of lymphoma in rheumatoid arthritis. For this presentation I would like to introduce Dr. Alan Silman, rheumatologist and epidemiologist from the Medical Research Council of the United Kingdom, who is currently the lead

investigator for the United Kingdom National RA Registry.

Dr. Silman is Professor at the University of Manchester and will share some of his thoughts on the epidemiology of lymphoma in patients with RA. Dr. Silman.

DR. SILMAN: Thank you. Much of what I am going to say today, I guess, has already been mentioned. But considering an estimate of the incidence or risk of lymphoma in etanercept treated patients, ideally what we want to be able to do is to separate out various components, the background population risk, the risk attributable to rheumatoid arthritis *per se*, whether there is an increased risk attributable to severe RA, and also what really hasn't been mentioned this morning but I think is important is the increased risk which is attributable to prior exposure in etanercept treated patients with other immunosuppressive agents, for example, azathioprine and methotrexate.

Also, increasingly when one is evaluating the risk of lymphoma, or indeed any other adverse

event, in a group of patients treated with a biologic agent, we have to take account of the fact they may have been treated with another biologic agent.

We have already heard outlined this morning the standardized incidence ratio being the ratio of the observed to the expected number of cases. In fact, it has been pointed out that this might not be the most appropriate descriptor to describe the increased risk either the public at large or to health care providers.

I'd just like to put forward two alternatives for you to consider. The first is what an epidemiologist might call the absolute risk or the risk attributable in this case to etanercept therapy. If we were able to calculate in those patients treated with etanercept what their expected risk was based on the fact of their disease, the severity of disease, and their other treatment, what is the increased risk due to the fact of treatment?

Another way of looking at the same data is to calculate the attributable risk fraction. This says we've got an observed risk. What proportion of

that is actually due to what we are interested in?

Now this example might help. These are made-up data, but in order to give some clarity to what I have previously said.

Suppose in the etanercept treated cohort we have an observed incidence of three cases of lymphoma per 1000 patient years of treatment. In that group we might have expected, based on all the other factors I have outlined, an expected incidence of two per 1000. Therefore, the incidence ratio is 3 over 2, which equals 1.5.

I suspect it might be more useful to look at the absolute risk where you are just subtracting the expected from the observed, which allows you to say exactly for each 1000 patient years of treatment there is an additional one case.

Alternatively, by calculating that as a fraction of the overall risk, one can say, for example, in this example, that given the number of lymphomas in etanercept treated patients, if these data were real, a third of them are attributable to the etanercept, and two-thirds are attributable to

other factors.

I think the challenge for all of us is to try and get the right numbers in order to give these answers.

When talking about the factors that we need to think about -- and again, many of these have already been mentioned, the background incidence in the comparable population, and I'll come back to that -- we do need accurate exposure data, and I think completeness of follow-up is important.

It is quite easy in all these studies to lose patients at follow-up, an epidemiological construct we call right censorship, and that is important, because if we are selectively losing, for example, the milder patients or those individuals without problems, we may be selectively concentrating the adverse events in those people we do follow up.

We have already talked about the differences in the population and also aspects of disease and treatment that might influence risk.

I think Dr. Tarone has very nicely talked about how important it is to have a way of

ascertaining all cases and to validate all cases.

There are some other methodological issues. Again, many of these have been already considered. Lymphomas are rare, and risk estimates do have wide confidence intervals, though I do share the point that it is difficult to get over a confidence interval to even graduate students, never mind the population.

The issue of surveillance bias: Are early lymphomas that we are picking early during the course of follow-up -- are they likely to be due to the drug or due to better detection? Ideally, if we have sufficient numbers, we could look for a dose response effect, as has been done, for example, in relation to azathioprine? Is there evidence of increasing risk in people, depending on the size of the dose, duration dose, etcetera?

The other point of crucial importance is the influence of length of follow-up. follow-up periods may not have equivalent risk. When you talk about the risk per 1000 patient years or patient months of observation, it may be very different if

that period of observation is concentrated, for example, in the first 12 or 24 months rather than later periods.

One of the problems is we have relatively small numbers, but as our experience increases, we will be allowed to dissect out what are the periods of greatest risk.

I just want to discuss a little of the data with you on the variation in lymphoma incidence in RA populations. I don't believe there is any doubt that there is an increased risk in lymphoma in patients with rheumatoid arthritis independent of the treatment they have received, and all these studies come from the pre-biologics era.

I think what is interesting and maybe the take-home message here is that there is considerable variation even within the RA population. Now some of this, particularly those two high bars at the right, might represent individuals with severer disease than in the other bars, which are more attempt at a population derived cohort. But the message is clear. There possibly isn't one estimate of increased risk

of lymphoma in RA.

What I have done here is to pick out the four largest population based studies and attempted to derive a pooled estimate, as far as one can tell, in relation to the lymphoma risk in the background RA population.

These are studies from very different parts of the world, from Europe and from North America. Actually, the dramatic thing -- and in epidemiological terms, believe me, it is dramatic -- the similarity in risk are twofold with a fairly narrow band of upper and lower confidence intervals.

I think these data are persuasive that, if one goes to a population level, you do find this increased risk.

I'd just like to finish by just letting you know what is happening in Europe and in the U.K. in particular. In the U.K. now, physicians can only prescribe anti-TNF agents if they register them with the National Biologics Register, which is based in my own group in Manchester.

We are attempting to follow up both

cohorts treated with etanercept as well as the other agents compared with cohorts that could be treated, if we had the funding, but are not, and allowing us to match for the various disease and other treatment characteristics.

We are also combining this effort, as I think you have already heard from both Dr. Fischkoff and Dr. Burge, with other registries in Europe to try and get the larger numbers. But I think, in answer to a question you have not yet raised, my guess is the answer to this might not come for another three of four years.

Thank you very much. I think Dr. Burge is going to continue.

DR. BURGE: Thank you, Dr. Silman. We would now like to discuss the available data on lymphoma from etanercept clinical trials in the post-marketing experience. We will review the histology of lymphoma reports, and state the conclusions that can be drawn from this data.

Recall that an accurate estimation of SIR is dependent on precise ascertainment of incident

cases and the corresponding period of observation. Clinical studies provide the only opportunity to accurately estimate the SIR for this treated population.

In the etanercept clinical trials program, six cases of lymphoma have been reported on study. Utilizing the SEER database applied to a comparable cohort in the general population, one would expect 2.59 cases, yielding an SIR of 2.31. Note that the confidence interval includes 11, and the point estimate is similar to the 2.2 represented by Dr. Silman.

Note that this table here will also act as a reference in the next three slides for further analysis.

Etanercept has been evaluated in a broad range of populations. The vast majority of our patients, regardless of disease duration, had moderate to severe RA with mean tender and swollen joint counts in the high twenties. Other than the early RA study, patients had typically failed three or more DMARDs and had a mean disease duration of over ten years.

Evaluating the lymphoma SIR in early and in more advanced disease, we obtained numbers that are actually quite similar. Additionally, time to onset is dispersed with a range of 0.4 to 4.8 years.

Three additional lymphomas have been reported after study completion in patients previously treated with etanercept in clinical trials. As the period of post-trial observation for all patients is not known, an accurate denominator cannot be calculated, and we cannot derive an accurate SIR. However, if we consider only the patient time on study and use the expected number of 2.5, this conservative SIR is 3.47.

The SIR calculated in the previous slides have been relative to the general population. Using the benchmark of 2.2-fold increased risk described by Dr. Silman for the general RA population, we multiplied the 2.59 expected cases by the 2.2 and derived an expected number of 5.7 for the RA population. The SIR for this analysis is 1.05.

Recognize that patients treated with etanercept do have more severe disease than the

general RA population, which is known to confer greater risk and is not included in this analysis.

Lymphomas have been described in post-marketing reports in patients who have received etanercept therapy. The reporting rate is 0.3 cases per 1000 patient years. The background incidence in the general population is 0.3 per 1000 patient years, and utilizing the adjustment of 2.2 would yield an incidence for the RA population of 0.66 per thousand patient years.

As would be expected in a predominantly RA population, most of the reports are from women. The mean age is 61, and the majority of patients were previously treated with methotrexate.

We have carefully tracked these reports since commercialization. Shown here are the rate of reports by report date, in blue, and by diagnosis state, in -- excuse me, report date, in yellow, and diagnosis date, in blue.

As one can see, the reporting rate for lymphoma presented here in six-month intervals is stable over the four years of commercial experience.

We have evaluated the distribution of subtypes of lymphoma in the clinical trials and post-marketing experience. As can be seen in this slide, the distribution, 14 percent of Hodgkin's and 86 percent non-Hodgkin's, is nearly identical to that expected in the general population utilizing rates in the SEER database.

We additionally obtain, whenever possible, pathology reports on cases of lymphoma and have them reviewed by an oncologist or a hematopathologist for classification into histologic subtypes. Histopathology was obtained for almost 70 percent of all these reports.

The distribution of the NHL subtypes is compared here to the distribution reported in the literature for a rheumatoid arthritis population and a non-RA control group. The distribution of histologic subtypes is similar in all three groups.

Immunosuppression such as that seen following organ transplantation is associated commonly with an increase in the proportion of diffuse large B Cell lymphomas, and this pattern is not seen with

etanercept therapy, as shown on the first line of this slide.

In conclusion, lymphoma reports with etanercept are rare. A comprehensive pharmacovigilance program has been in place for four and a half years, and the rate of lymphomas observed in clinical trials is consistent with the expected rate for RA patients with an SIR of 2.3.

Our post-marketing experience is compatible with the clinical experience, and the distribution of histologic subtypes is as expected. With six years of sustained therapy, we see no evidence of an increase in lymphoma incidence.

Amgen supports proactive communication to health care providers and has initiated processes to assure timely dissemination of this information. We, therefore, in the latter part of 1002 submitted a proposal to the FDA to represent the lymphoma experience in the adverse events section of the etanercept package insert.

The purpose of this proposal was twofold: First, to inform physicians that the background

incidence of lymphoma in RA was increased; and, two, that the observed incidence of lymphoproliferative disorders from clinical trials and post-marketing reporting rate are similar to that expected.

We additionally have presented this data at scientific meetings for rheumatologists at ACR and at EULAR, and we believe that the programs we have in place, long term clinical trials, observational studies, further characterization of epidemiology, and continued safety surveillance are an important part of our commitment to patients.

In 2002 the product label was updated from information from the etanercept heart failure program, which was designed to test the hypothesis that etanercept was effective in treating chronic heart failure. We would like to share some of the observations from this study.

The etanercept CHF program consisted of over 2000 patients in two studies. The global trial called RECOVER included three treatment arms, as outlined by Dr. Unger earlier, a placebo group, Enbrel-25 once a week, and twice a week. I apologize.

I'm describing the lower part of the slide. And the RENAISSANCE trial included three treatment arms also, the placebo, 25 twice a week, and 25 three times a week.

The analysis of the combined studies was called RENEWAL. The program had in place predefined interim analyses for safety and efficacy. One of these analyses, a futility analysis, specified that studies were to be discontinued if meaningful clinical benefit was not likely to e demonstrated. In March of 2001, the futility endpoint was met, and the studies were stopped.

The primary efficacy endpoint of RENEWAL, the analysis of combined studies, was the time to all-cause mortality and CHF hospitalization. This morbidity and mortality endpoint was also evaluated in the individual studies, but was not the primary endpoint.

As you can see here, each of the treatment groups is shown with the relative risk to placebo within the study. Note that the confidence intervals of all analyses include 1, and that in the RENAISSANCE

study, the relative risks trend toward worse heart failure outcomes in patients treated with etanercept.

These observations are not duplicated in the RECOVER study, and the combined analysis, RENEWAL, had a relative risk of 1.10.

A number of characteristics that were known to have significant impact on heart failure outcomes were prospectively identified as covariates relevant to the interpretation of these trial findings.

In the RENAISSANCE study, randomization of patients resulted in imbalances of some of these characteristics in favor of the placebo group. For example, the percentage of patients with a history of atrial fibrillation or atrial flutter is 29 percent in the placebo group and 36 percent in each of the etanercept groups.

The left side of this slide represents the data previously shown. On the right side of the slide is the relative risk after adjustment using Cox proportional hazards regression for the predictive and imbalance covariates. The trends seen in the

RENAISSANCE study have diminished, and the combined analysis results in a relative risk of 1.01.

This slide represents a secondary endpoint of time to all cause mortality. The findings of this endpoint are similar to those of the primary endpoint shown previously. There was a trend in worse outcomes in the RENAISSANCE study that was not duplicated in RECOVER. Again, after accounting for covariates, the trends do diminish, and the relative risk of the combined analysis is 0.96.

In conjunction with review of the data from patients with underlying heart failure, we also analyzed heart failure occurrence in rheumatic disease studies, patients who were not known to have underlying heart disease.

The number of subjects developing new onset heart failure was similar, and was the same in the etanercept and control arms of the controlled trials. As much of our experience is from open-label observations where no comparator is available, we have used benchmarks from the literature to calculate the expected number of cases.

The number of cases of new onset CHF treated with etanercept in rheumatic disease trials was seven, compared to the 15.2 expected. So the rate of new onset CHF is not increased in rheumatic disease trials.

Despite no clear evidence of deleterious effect of etanercept in heart failure, it was important to communicate these findings to health care providers, particularly rheumatologists. On that basis, in May of 2002 we added a precaution in the product label. Additionally, the data from the heart failure trials was presented at scientific meetings for cardiologists and rheumatologists.

In conclusion, two large heart failure studies were discontinued due to lack of efficacy and, although one of the two studies showed a trend toward worse heart failure outcomes, the second trial did not. Overall, there is no clear treatment effect of etanercept in heart failure patients.

Additionally, there is no evidence from rheumatic disease trials that etanercept increases risk for CHF. However, we chose to inform prescribers

this important information through labeling and at scientific meetings.

We have built a foundation of extensive, long term safety experience with etanercept. This experience encompasses the clinical trials previously discussed here in this presentation, complemented by observational and long term studies, epidemiologic studies, and ongoing safety surveillance. Amgen is committed to proactive communication.

This table summarizes the initiatives that are being conducted by Amgen and Wyeth. We anticipate that these programs going forward will provide further insights into the safety issues discussed today.

The long term clinical trials where we have already accrued five years of experience will be conducted for at least ten years. Additionally, the ongoing RADIUS program will prospectively observe 10,000 RA patients for five years in the clinical practice setting.

Furthermore, a JRA registry has been established in the U.S., and national RA registries have been implemented in Germany, Sweden, and the

United Kingdom.

This comprehensive program will advance the understanding of etanercept and underscores Amgen's and Wyeth's commitment to patient safety.

Three-year safety and efficacy data from our long term trials have been included in our product label, and we have submitted to the FDA four-year data. We plan to submit data regarding five years of etanercept experience to the FDA this summer. These data have been included in these presentations.

Although we have nearly fulfilled our post-marketing commitment to the FDA, we will continue to follow these patients for an additional five years.

In summary, the soluble receptor etanercept has unique structure, mechanism of action, and pharmacokinetic that, we believe, make etanercept a unique therapeutic. Etanercept has an established track record with over nine years of experience in treating rheumatic disease patients and four years of clinical practice experience.

This extensive experience, along with a robust pharmacovigilance program, has allowed us to

characterize the etanercept safety profile. With its highly favorable benefit/risk profile, etanercept remains a very important contribution in the therapy of patients with rheumatic diseases. Thank you.

CHAIRMAN ABRAMSON: Thank you very much. Are there questions? Dr. Makuch?

DR. MAKUCH: Just a few questions. One relates to the futility. I mean, it really seemed like a very one-sided hypothesis, namely -- I think I got it right -- is that, if meaningful clinical benefits could not be achieved, then you would stop the study.

On the other hand, if one is looking at a safety concern, that seems to be not the proper hypothesis to look at. You would like to know whether there is clinical benefit or perhaps clinical harm.

So it then gets to the second comment, that RENAISSANCE was your longer study, and then you went on to indicate that the RECOVER study did not replicate in some sense the RENAISSANCE results.

I guess I'm not surprised that that is the case, because the RECOVER study had a very much

shorter median follow-up period. I think we heard earlier that it was 5.7 months compared to over a year for the RENAISSANCE study.

The final comment then is with respect to the covariates, you show the analyses again trying to make any marginal trends go away, that once you include covariates then, even for RENAISSANCE, the results really were very null.

I think we are all aware of the problems that one has when throwing in lots of covariates into a model. So my general comment is how was it determined that these studies were stopped early and that, it appears to me -- I have a little discomfort with respect to concluding that, one, the RECOVER study did not replicate the RENAISSANCE -- I'm not surprised -- and two, with respect to the one-sided hypothesis seemed to be used for the futility?

DR. BURGE: There were several pre-defined analyses that the data monitoring committee were charged with evaluating on an ongoing basis when they had these data monitoring committee meetings, and there were discussions about, or rules for stopping

for efficacy as well as stopping for safety.

The efficacy rule was that the study would be discontinued if there was no evidence -- if it was not likely that there would be the ability to show at least a ten percent benefit with etanercept, and it was on that basis that the study was discontinued.

The committee very specifically, when they did their review, mentioned that it did not meet their threshold for discontinuing the study on safety grounds.

CHAIRMAN ABRAMSON: Dr. Elashoff.

DR. ELASHOFF: Yes. This question is for Dr. Silman. The attributable risk fraction as defined on the first slide and as done in the example on the second slide do not agree. So perhaps you could say which is the correct formula. If it's the first one, then it's just the SIR minus 1.

DR. SILMAN: Sorry. Can I have the slide back on? I sit possible to have the slide back on?

DR. ELASHOFF: So is this the correct formula?

DR. SILMAN: Just let me check. It's the

observed -- Sorry, it's observed minus expected. So that -- It's observed minus expected over the observed.

DR. ELASHOFF: So this formula is incorrect then on this one?

DR. SILMAN; Yes. Sorry, I apologize for that. Thank you. Yes.

CHAIRMAN ABRAMSON: Dr. Blayney.

DR. BLAYNEY: In the -- Directed to the congestive heart failure experience with etanercept, you have about 2000 patients that you followed for half a year to a year. What was the lymphoma risk observed in those people, and the tubercular infection rate observed in -- tuberculosis infection rate observed in those people who are not presumably previously exposed to DMARDs or other kinds of immunosuppressives?

DR. BURGE: The first part of your question was referring to -- I'm sorry. There's so many parts to that, I lost track.

DR. BLAYNEY: The adverse effects in a congestive heart failure trial presumably includes

secondary --

DR. BURGE: Lymphoma, infections, TB, yes. Lymphoma, if you calculate an expected rate of lymphoma in the congestive heart program, the entirety of that would be age, sex, match adjustments. The expected is 0.7 lymphomas. There was one lymphoma observed in that experience.

As far as all serious infections, it actually was actually even across all treatment groups actually in both trials.

There was one case of tuberculosis in the European trial.

DR. BLAYNEY: Thank you.

CHAIRMAN ABRAMSON: Yes, Dr. Manzi.

DR. MANZI: I just have two fairly direct questions. The first is: In relationship to looking at congestive heart failure in the RA trials, I think that's very different than in the trials where you are specifically entering people with obviously active congestive heart failure. My guess is that there may have been some selection or exclusion of patients with either active or comorbid conditions in the RA trials,

so that the population may be very different than how it will be used post-marketing. Is that --

DR. BURGE: Yes. The clinical trials had exclusion for severe uncompensated heart failure, but having any heart failure was not excluded. We primarily looked at the rheumatoid arthritis and the other rheumatic disease trials to look for new onset heart failure, because certainly the database we have from the 2000-patient clinical program in heart failure is much more meaningful to evaluate exacerbations of heart failure than any experiences we have in this small number of cases in the rheumatic disease trials.

DR. MANZI: And my last question is for Dr. Silman. That is: When you give us the SIR for RA patients in general with this twofold increased risk, I am assuming that is not independent of prior immunosuppressive exposure.

DR. SILMAN: That's a very good question. I mean, the data that do exist actually don't give us that information. Interestingly, the study that showed the highest risk, which was the smallest study

from the United Kingdom, actually was independent of immunosuppressive data, but the studies that I presented, the larger studies, there are not data available.

CHAIRMAN ABRAMSON: Dr. Burge, can I just get a clarification of the numbers? You saw six lymphomas during the randomized trials, and then you discussed 70 subsequent to that. Were they in your registries and open-label extensions or were some of those MedWatch type reports?

DR. BURGE: The 70 was the post-marketing experience of spontaneous and facilitated reporting.

CHAIRMAN ABRAMSON: Separate from registries that you had yourselves?

DR. BURGE: It would include anything other than the clinical trials.

CHAIRMAN ABRAMSON: Thank you very much.

The next presentations will be by Centocor, and Dr. Boscia will make the first presentation.

DR. BOSCIA: Well, the good news is I promise to only spend one sentence on SEER and one

sentence on SIR. I promise.

Good morning. My name is Dr. Jerry Boscia. I am Vice President of Clinical Research & Development at Centocor. On behalf of Centocor and Johnson & Johnson, I would like to express appreciation for this opportunity to present information on REMICADE, or infliximab.

I would particularly like to express appreciation to Dr. Jeffrey Siegel at the FDA who we occasionally drive crazy. But of course, he never drives us crazy.

REMICADE is a monoclonal antibody that is specifically directed against human tumor necrosis factor alpha. After this brief introduction, I will be providing some background information with regard to REMICADE's safety profile.

Specifically, I will cover the following topics: Lymphoma; other malignancies; tuberculosis; opportunistic infections; and heart failure. I will spend the majority of my time on lymphoma, for obvious reasons. If you have questions on safety topics not addressed by me, we will be happy to answer them.

Dr. Tom Schaible will then summarize Centocor's ongoing and planned studies and registries for the continuing characterization of REMICADE's safety profile. He will briefly discuss REMICADE's efficacy and have some concluding remarks.

We have a short time to present our information, but in case anyone has additional questions, we have with us today several consultants who can help answer any questions. They are: Dr. Roger Cohen, a hematologist/oncologist from the Fox Chase Cancer Center; Dr. Susan Fisher, an oncologic epidemiologist from the University of Rochester; Dr. Stephen Hanauer, a gastroenterologist from the University of Chicago; Dr. Milton Packer, a cardiologist from Columbia University; Dr. Paul Stang, an epidemiologist from Galt Associates; Dr. William ST. Clair, a rheumatologist from Duke University; and finally, Dr. Frederick Wolfe, a rheumatologist from the Arthritis Research Center Foundation.

I would like to spend just a few minutes reminding everyone of the burden of disease with regard to rheumatoid arthritis and Crohn's disease.

As an infectious diseases physician -- that's my training -- I sometimes have to remind myself. So for the non-rheumatologists and non-gastroenterologists in the room, I thought I would just take a few minutes to do this.

Upwards of 90 percent of patients with aggressive rheumatoid arthritis develop significant disability within 20 years of diagnosis. Furthermore, the life expectancy of patients with rheumatoid arthritis is reduced compared with the general population.

Crohn's disease is a debilitating disease, mostly affecting young adults. In about half of patients it has a detrimental impact on patients' ability to work and/or their productivity at work. As many as 90 percent of patients with Crohn's disease require surgical intervention, and most of them require additional surgeries.

REMICADE is indicated for patients with rheumatoid arthritis and Crohn's disease who have had an inadequate response to conventional therapies. During Dr. Schaible's brief discussion of efficacy

towards the end of this presentation, you will see that REMICADE fulfills previously unmet medical needs with its profound benefit in a majority of patients.

REMICADE as a potent biologic also has safety issues. Centocor has been, and continues to be, diligent in characterizing REMICADE's safety profile. We presented a safety assessment of REMICADE to this committee in August 2001. Today we will update the committee with new data from our clinical trials, large registries, and spontaneous adverse event reports.

Centocor has completed 15 clinical trials with REMICADE in patients with rheumatoid arthritis and Crohn's disease, encompassing approximately 1700 patients treated for almost 3500 patient years. An additional 14 trials are ongoing in patients for a variety of diseases, encompassing about 3100 patients treated with REMICADE.

We estimate that, through August 2002 which was the last cutoff date for reporting to worldwide health authorities, 365,000 patients for about 554,000 patient years of exposure had been

treated commercially with REMICADE worldwide. This number of patients treated is now well over 400,000.

I will now review our data examining the risk of lymphoma and other malignancies associated with REMICADE treatment. As reviewed in the briefing document, an increased risk of lymphoma is associated with having rheumatoid arthritis or Crohn's disease.

Comparisons of lymphoma risk in these populations are typically made with age, race, gender matched, general population from the Surveillance Epidemiology and End Results or SEER database.

Lymphomas are more common in patients with rheumatoid arthritis compared with the general population, as demonstrated by standardized incidence ratios or SIRs of 2 to 3, as reported in the literature. Elevated relative risk is associated with greater inflammatory activity, as much as a 26-fold increase, poor functional class, and involvement of both the small and large joints.

Use of conventional immunosuppressants such as azathioprine have also been associated with increased risk. Although the epidemiologic data

supporting increased risk of lymphoma in Crohn's disease is not as compelling as for rheumatoid arthritis, the preponderance of studies suggests an association.

This table summarizes number of patients, patient years of follow-up, observed numbers of lymphomas, and SIRs for REMICADE clinical trials in rheumatoid arthritis. The assessment of SIRs for lymphoma is based on a comparison with the number of lymphomas expected in an age, race, gender matched, general population from the SEER database.

This is not as relevant a comparison as it would be against a population of patients with rheumatoid arthritis or, better yet, against a rheumatoid arthritis population with a similar level of disease activity as in the REMICADE clinical trials.

In contrast to our other analyses, this table also includes our recently completely trial in patients with early rheumatoid arthritis in order to show the differences between various rheumatoid arthritis populations.

For all REMICADE arthritis studies combined, the SIR for REMICADE treated patients is 6.4. We observed that no lymphomas occurred in a methotrexate naive early rheumatoid arthritis population who received REMICADE, compared with four lymphomas in a disease modifying anti-rheumatic drug or DMARD resistant high disease burden population, studied in our other rheumatoid arthritis studies.

These findings are consistent with the epidemiologic data I presented on the last slide. The SIRs for patients who received placebo are all zero. However, please note that the placebo patient years of follow-up is only 18 percent of the REMICADE patient years of follow-up in the DMARD resistant rheumatoid arthritis population, the group in which all four of the lymphomas occur.

Although the SIRs are greater for the REMICADE treated patients compared with the placebo treated patients, the 95 percent confidence intervals are wide and overlap.

This table summarizes the same information as the last one did for lymphomas, except this one

does it for REMICADE clinical trials in Crohn's disease, and then for all REMICADE studies from this and the last slide combined.

For all Crohn's disease studies, the SIR for REMICADE treated patients based on two cases of lymphoma is 8.7. The SIR for patients who received placebo is zero. However, please note that the placebo patient years of follow-up is only six percent of the REMICADE patient years of follow-up.

For all rheumatoid arthritis and Crohn's disease studies combined, the SIR for REMICADE treated patients is 7.0. Although the SIR for patients who received placebo is zero, the placebo patient years of follow-up is only 17 percent of the REMICADE patient years of follow-up.

Once again, the SIRs are greater for REMICADE treated patients compared with placebo treated patients, but the 95 percent confidence intervals are wide and overlap.

For those in the audience who wish to know the incidence of lymphomas in our clinical trials, I present this table -- in other words, if you prefer

incidence rather than SIRs.

These are shown for all REMICADE rheumatoid arthritis studies, all Crohn's disease trials, and both combined. Please note that the incidence is per 1,000 patient years of follow-up.

At study entry, the four patients with moderately to severely active rheumatoid arthritis who developed lymphomas had long disease duration, substantial joint involvement, and significant elevated sedimentation rates. All of these are factors associated with increased risk of lymphoma.

This figure summarizes the latency in months from first infusion to diagnosis, as shown with the yellow bars, REMICADE dose and number of infusions -- the number of infusions are shown as orange arrows underneath the yellow bars -- and other medications received for the four patients with rheumatoid arthritis who developed lymphoma.

The first three of these four cases were reviewed at our presentation to the FDA Gastrointestinal Advisory Committee meeting in 1998 when REMICADE was approved for Crohn's disease -- not

approved; when it was recommended for approval. Sorry about that.

The fourth case is new since that time. The four cases had a diverse histologic profile. One lymphoma was high grade, the grade most commonly observed in the setting of immunosuppression. The other three were not high grade and included an indolent lymphoma, a mantle cell lymphoma, and a Hodgkin's lymphoma.

No apparent relationship to REMICADE exposure was observed, with the third patient in this figure having received only a single dose of 1 mg/kg. Patients two and four had received azathioprine in their past, and the fourth patient started receiving etanercept about three months prior to diagnosis of lymphoma.

This figure summarizes the same information as the last one, except this one does it for the two patients with Crohn's disease who developed lymphomas. The first of these two cases was also reviewed at that 1998 FDA Gastrointestinal Advisory Committee meeting. The second case is new

since that time.

These cases also had diverse histology. One of these lymphomas was an intermediate grade B-cell lymphoma of histology that can occur in the setting of immunosuppression, and the other was an NK lymphoma. Both patients received only a single dose of REMICADE, and both were also receiving azathioprine.

Now this could be important. Unfortunately, we have Dr. Wolfe here with us here today. As we reviewed in our presentation to this committee in August 2001, we are supporting Dr. Frederick Wolfe's national data bank for rheumatic diseases to obtain long term follow-up for safety and outcomes in patients receiving commercially supplied REMICADE.

Dr. Wolfe's extensive database in over 18,000 patients with rheumatoid arthritis enables the comparison of REMICADE treated patients with patients who have not received REMICADE. The patients in the registry are from 908 rheumatology practices in the United States. Dr. Wolfe's group captures data twice

yearly using a mailed questionnaire.

Several parameters are assessed, including adverse events and outcomes. There is a validation process to maximize accuracy and reliability. The registry retains a high retention rate of its patients with approximately an eight percent attrition rate each year.

The same information that I summarized earlier for the clinical trial lymphoma cases is summarized in this and the next table for the lymphoma cases in Dr. Wolfe's registry. Again, this uses the SEER database to determine the expected number of cases.

This table shows the SIRs for lymphoma patients who received no methotrexate or anti-TNF therapy, those who received methotrexate but no anti-TNF therapy, and those who received REMICADE and/or etanercept. Please note that three patients received both REMICADE and etanercept and are represented in both the REMICADE and etanercept lines.

When evaluating the SIRs on this slide, please note that the patients receiving anti-TNF

therapy are probably at greater risk for lymphomas compared with those not receiving anti-TNF therapy, due to greater levels of disease activity refractory to standard treatment. So when you look at those, 1.3, 1.5, 2.6, and 3.8, remember that.

We also reviewed with this committee in 2001 our plan to develop the Crohn's therapy resource evaluation and assessment tool or TREAT registry. This registry has now enrolled 5,000 patients, including both patients treated and not treated with REMICADE.

The TREAT registry enrolled patients with Crohn's disease who were 18 years or age or older and were willing to participate for at least five years. Patients completed a health status questionnaire at baseline, and they do so every six months. Data collected includes adverse events and outcomes.

Follow-up data is now available in approximately 1100 REMICADE treated patients, and 1300 patients not treated with REMICADE. The number of reported lymphomas is shown here. One lymphoma has been reported in a REMICADE treated patient, and one

has been reported in a patient not exposed to REMICADE.

Spontaneous adverse event reports of lymphoma are summarized in this slide. A total of 71 lymphomas were reported in patients with rheumatoid arthritis, Crohn's disease, and other diseases through August 2002, the last cutoff date for reporting to worldwide health authorities.

When Dr. Cote presented this information earlier -- Dr. Cote from the FDA -- he mentioned 95 cases of lymphoma. His cutoff, though, was December of 2002, and that explains the difference. Our numbers match his through December.

In summary, lymphomas are common in patients with rheumatoid arthritis -- are more common in patients with rheumatoid arthritis compared with the general population, as demonstrated by SIRs of 2 to 3. The risk increases with increasing severity of disease.

An SIR of 6.4 for lymphoma was observed in REMICADE treated patients compared with the general population from the SEER database in our clinical

trials. However, the lymphomas occurred in patients who had known risk factors for elevating lymphoma risk. These included high inflammatory activity, high disease burden, and long term exposure to immunosuppressive agents.

An SIR of 2.6 for lymphoma was observed in REMICADE treated patients compared with the general population from the SEER database in Dr. Wolfe's registry. Based on all this, the rates of lymphomas may not be greater in the REMICADE treated rheumatoid arthritis and Crohn's disease populations compared with populations with similar levels of disease activity who do not receive REMICADE.

Centocor remains committed to continue to examine the potential lymphoma risk in clinical trials, large registries and post-marketing pharmacovigilance. We look forward to the FDA Arthritis Advisory Committee's and FDA's deliberation, assessment, and guidance on the best approach to studying the potential risk of lymphoma with anti-TNF therapy, and the best means to communicate to treating physicians in our prescribing information.

We feel current evidence is insufficient to reach conclusions on whether REMICADE increases the risk of lymphomas.

We will now -- I will now -- I will now briefly review our clinical trial and spontaneous adverse event reports of non-lymphoma malignancies in rheumatoid arthritis and Crohn's disease.

To date, epidemiologic studies in large rheumatoid arthritis cohorts have not demonstrated an increased risk of non-lymphoma malignancies in this disease. Longstanding Crohn's disease predisposes to intestinal malignancies, with the risk of colon carcinoma for Crohn's colitis thought to be similar to ulcerative colitis.

This table summarizes the same information for non-lymphoma malignancies in REMICADE clinical trials as I showed earlier for lymphomas. Once again, this uses the SEER database to determine the expected number of cases.

For all rheumatoid arthritis studies, all Crohn's disease studies, and all studies combined, the SIRs for REMICADE treated patients approximate one.

They are no greater than the SIRs for placebo treated patients, despite the fact that the placebo patient years of follow-up are only 6 to 18 percent of the REMICADE patient years of follow-up. Admittedly, the number of non-lymphoma malignancies in the placebo treated patients is small.

Robby, can you go back, please? When Dr. Liang from the FDA presented this data, he presented it with the ASPIRE trial, and we have that, and we can present it that way also. The reason we chose not to include ASPIRE in this analysis is because it's still blinded, and we didn't know which groups, of course, to put the five malignancies that exist and have occurred in ASPIRE. We didn't know where to put them.

Dr. Liang presented the worse case scenario, and we can also put that slide back up, if the committee would like to see it once again.

In our post-marketing commercial experience, 354 non-lymphoma malignancies have been reported in patients with rheumatoid arthritis, Crohn's disease, and other diseases through August 2002. This includes 230 in patients with rheumatoid

arthritis and 68 in patients with Crohn's disease.

Taken together, our clinical trial data and spontaneous adverse event reports are insufficient to reach conclusions on whether REMICADE increases the risk of non-lymphoma malignancies.

The topic of tuberculosis was covered in detail with this committee in August 2001. Just prior to that meeting, Centocor added a box warning addressing tuberculosis in our prescribing information.

Associated with this was the mailing of a Dear Health Care Professional letter. Also, during August and September of that year, we implemented our tuberculosis medical risk management education program. This involved about 7500 rheumatologists and gastroenterologists in the United States.

Our follow-up of this program indicates that most of these physicians evaluate patients for latent tuberculosis infection with a tuberculin skin test prior to therapy with REMICADE.

Also, there has been a decreased number of spontaneous reports of tuberculosis, despite a steady

increase in the number of patients, including new patients, treated with REMICADE. Before Dr. Miles Braun has chest pain, I should mention that we realize that part of this effect could be due to a decrease in reporting efficiency.

This table depicts the worldwide reports in REMICADE treated patients for a variety of viral, bacterial, and fungal opportunistic infections reported during post-marketing surveillance through August 2002. Potential confounding factors for the development of opportunistic infections include the fact that patients with rheumatoid arthritis being treated with REMICADE also received methotrexate, since REMICADE is labeled for combination use with methotrexate.

Furthermore, patients with rheumatoid arthritis as well as patients with Crohn's disease typically receive other additional immunosuppressive agents, such as corticosteroids, azathioprine, 6-mercaptopurine, and others. Often, patients are receiving two or more of these immunosuppressants.

The cases of histoplasmosis and

coccidioidomycosis have, for the most part, occurred in the Ohio, Mississippi River Valleys and southwest Untied States respectively where histoplasmosis and coccidioidomycosis are endemic.

For patients who have resided in regions where histoplasmosis and coccidioidomycosis are endemic, the benefits and risks of REMICADE treatment should be carefully considered before initiation of REMICADE therapy.

With regard to all of these opportunistic infections and tuberculosis, patients should be monitored for signs and symptoms of infection while on or after treatment with REMICADE. The route of administration of REMICADE fosters regular physician-patient interaction and, therefore, very close follow-up.

Now I would like to turn our attention to heart failure. I know you've been through this already, but I'll be brief.

The ATTACH trial was a randomized, placebo controlled, Phase 2 study designed to evaluate the effect of REMICADE in patients with Class III-IV heart

failure due to systolic dysfunction. One hundred fifty patients were randomized to receive placebo, 5 mg/kg of REMICADE or 10 mg/kg of REMICADE at zero, 2 and 6 weeks.

The protocol specified follow-up period was 28 weeks. In addition, survival status at one year was determined for all patients. This table displays the number and Kaplan-Meier rates of patients who were hospitalized for worsening heart failure at 28 weeks, and the number and rates who died through both 28 weeks and one year.

At 28 weeks the rates of hospitalization for worsening heart failure were similar in the placebo and 5 mg/kg groups, but increased in the 10 mg/kg group. At the same time point, mortality was increased in the 10 mg/kg group. By one year, there were similar death rates in the placebo and 5 mg/kg groups, with a persistent increase in the 10 mg/kg group.

The REMICADE prescribing information was updated by the company in march of 2002, at which time all patients in the ATTACH trial had completed 38

weeks of follow-up, but one-year mortality follow-up was still ongoing.

At that time, it was decided to contraindicate REMICADE at any dose in patients with Class III/IV heart failure. Although no data were available in patients with Class I/II heart failure, avoidance of REMICADE doses greater than 5 mg/kg was recommended in these patients.

Now that complete results on the ATTACH trial are available, including mortality data through one year, we are discussing with Dr. Ellis Unger at the FDA the potential for further changes to the prescribing information.

Centocor and the FDA -- Somebody asked this question earlier, somebody on the committee. Centocor and the FDA have recently focused attention on new onset heart failure. That is the appearance of heart failure in patients with no known history of heart failure.

Reports of heart failure in clinical trials other than ATTACH have been infrequent. This is probably due, at least in part, to the exclusion of

patients with significant underlying cardiac disease at study start.

This table shows that, despite the approximately 20 percent less average follow-up in weeks for patients on placebo compared with those on REMICADE, there is no increase in new onset heart failure in patients treated with REMICADE compared with those on placebo.

As of October 2002 there were 158 spontaneous post-marketing reports of heart failure. Twenty-eight of these had no known history of heart failure, acute precipitating event or risk factor -- none of those. However, interpretation of these data is confounded by incomplete and, at times, conflicting information, as well as lack of a control group.

Centocor is presently discussing these spontaneous cases of new onset heart failure with the FDA.

I would now like to introduce the person who stands between you and lunch, Dr. Tom Schaible, Vice President of Medical Affairs at Centocor, who will summarize our plans for continuing to assess

safety in clinical trials and patient registries.

He will briefly discuss REMICADE efficacy and have some concluding remarks. Tom.

DR. SCHAIBLE: Thank you, Jerry, and thank you for putting me on the spot. I appreciate this opportunity to speak to the advisory committee as well.

In this presentation I would like to review with the committee our continuing commitment to obtaining long term prospective safety information in patients receiving REMICADE.

First, I will review our progress on commitments made at the August 2001 Arthritis Advisory Committee. These ongoing safety assessment programs include Phase III and Phase IV clinical trials, patient registries, and our long term follow-up program in clinical trials.

Secondly, I will review new safety assessment programs that we are undertaking. These will include programs to further expand our safety databases, as well as to obtain specific follow-up on lymphoma cases.

As I review these programs, all of which are collecting data in patients receiving REMICADE, you will see that many are designed to also include patients who have not received REMICADE. These data are important in helping to differentiate safety signals that may be associated with anti-TNF therapy from those that occur as part of the natural history of the disease.

In the next series of tables I will review the status of ongoing safety assessment programs, showing the status at the last committee meeting in August 2001 and the status as of last week.

This table reviews our Phase II and Phase IV studies in rheumatoid arthritis. The ASPIRE trial in early RA has completed enrollment of 1049 patients, and all of these patients have completed one year of study treatment.

The Phase IV START study, designed specifically toe valuate safety, and the iRAMT study evaluating methotrexate tapering have both completely enrolled patients since the last meeting.

Two Phase II trials in Crohn's disease,

the ACCENT I trial in active luminal Crohn's disease, and the ACCENT II study in fistulizing Crohn's disease had both completed enrollment at the August 2001 Advisory Committee meeting. Since that time, ACCENT I has received marketing approval for maintenance therapy in Crohn's disease, and for ACCENT II the BLA has been submitted and has received a priority review status from FDA.

At the last meeting we reported that Centocor is sponsoring two patient registries to evaluate long term safety in patients receiving commercially supplied REMICADE, one in rheumatoid arthritis and one in Crohn's disease.

We have now well exceeded our target of 5000 REMICADE treated patients in the National Databank for Rheumatic Diseases Registry. We have also recently achieved our target of 5000 REMICADE or non-REMICADE treated patients in the TREAT Crohn's disease registry.

We will continue to enroll patients in these registries to compensate for the expected attrition of some patients over time and maintain a

minimum of 5000 active patients in each registry.

As you saw in Dr. Boscia's presentation, both of these registries provided valuable data for evaluating the occurrence of lymphomas in REMICADE and non-REMICADE treated patients with these diseases.

When combining the safety assessment programs that I have just described, a substantial prospective safety database emerges. As of today, this includes approximately 13,000 patients who have received or are receiving REMICADE and approximately 15,000 disease matched non-REMICADE treated patients for comparative analyses.

I should also mention that this database includes our long term safety follow-up program which follows all patients who have participated in our clinical trials for a period of five years following their study participation. In August 2001 we committed to developing safety databases encompassing 12,500 REMICADE treated patients, and we have achieved that goal.

At the same time, we are also initiating new international patient registries to further grow

our safety databases. This includes the APART registry, an RA registry in the U.S. that will enroll another 2500 patients. With our colleagues at Schering Plough, our REMICADE marketing partner in Europe, we are participating in a consortium of existing RA registries in Spain, Germany, Sweden and the U.K.

Finally, also in collaboration with Schering Plough, we are creating a Crohn's disease registry in Europe that will enroll approximately 4000 patients, and follow them for five years. All of these registries will enroll and prospectively follow both REMICADE treated and non-REMICADE treated patients.

The registries will also provide valuable sources to obtain additional details on reported lymphomas. Importantly, we should be able to compare lymphoma profiles when REMICADE is given with or without other immunosuppressants, and also with patients who have not received REMICADE.

In more fully characterizing lymphomas, we will actively collect data on exposure and latency,

clinical presentation, histology, and EBV status, and treatment and response to therapy. We will also initiative surveillance in multiple health care delivery systems, such as HMOs, to further quantify lymphoma risk and contributing factors.

In considering risk management initiatives, we should recognize that REMICADE is used by a well defined set of physicians. REMICADE is used primarily by, and continues to be promoted to sub-specialists, namely rheumatologists and gastroenterologists.

We believe that sub-specialists are best able to make benefit risk decisions on the appropriate use of anti-TNF agents. In addition, the sub-specialist population can be readily targeted for risk management initiatives.

This was exemplified by the REMICADE TB education program that we conducted in August and September of 2001. This program targeted 7500 physicians who were responsible for treating over 90 percent of patients who were receiving REMICADE.

In conclusion, Centocor remains committed

to research and education regarding the safety of REMICADE. As we have done with TB, we will conduct risk management programs as specific safety issues arise.

With regard to safety assessment, Centocor continues to grow its prospective safety databases in rheumatoid arthritis and Crohn's disease. These include Phase III and Phase IV clinical studies, international patient registries, and a long term safety follow-up program.

As of today, safety follow-up in REMICADE treated patients and non-REMICADE treated patients is being conducted in nearly 30,000 patients. This knowledge base will continue to increase in the future. We expect these programs to provide approximately 100,000 patient years of prospective follow-up over the next five years in REMICADE treated patients.

Although most of our presentation today discussed risk, no benefit to risk profile can be addressed without some mention of benefit. Therefore, to close our presentation today, I would like to

briefly review some of the attributes of the efficacy of REMICADE in rheumatoid arthritis and Crohn's disease.

The ATTRACT trial was a Phase III, two-year, controlled study in patients with moderately to severely actively rheumatoid arthritis despite methotrexate therapy. After 30 weeks of treatment, which was the primary endpoint for signs and symptoms, all four REMICADE treatment regimens in combination with methotrexate produced reductions in the signs and symptoms of disease activity, as measured by the percentage of patients achieving ACR20 criteria. These were significantly greater than the reductions achieved by patients receiving methotrexate alone.

In ATTRACT the changes in the Van de Heijde modified Sharp Score were used to assess progression of structural damage due to rheumatoid arthritis over two years. The median changes from baseline in the total score at two years were 0.5 for all four of the REMICADE dose groups combined, and 4.3 for the methotrexate alone group.

Thus, there was little or no progression

of structural damage observed in the REMICADE treated patients over a period of two years.

REMICADE is the only agent approved for improving physical function in patients with rheumatoid arthritis. This figure presents the data on the improvement in physical function as measured by the Health Assessment Questionnaire or the HAQ Score averaged over the two years of the ATTRACT trial.

The lines represent the median improvement in the HAQ averaged over time bracketed by the inter-quartile ranges. In short, patients enrolled in ATTRACT who had longstanding disease and substantial impairment in function at baseline, when treated with REMICADE, had a statistically and clinically meaningful improvement in function compared with patients who were treated with methotrexate and placebo over two years.

The clinical benefit of REMICADE for Crohn's disease is substantial and unique. This was initially demonstrated in this Phase III trial in which patients with active luminal Crohn's disease who were not adequately responding to conventional

therapies were treated with one 5 mg/kg dose of REMICADE or placebo.

Four weeks later, over 80 percent of the treated patients achieved a definitive clinical response, and nearly half achieved clinical remission. The relevance of this benefit is underscored by the low placebo response rates observed.

The importance of REMICADE maintenance therapy for luminal Crohn's disease was demonstrated in our ACCENT I trial. The proportion of patients maintaining clinical remission at week 30 was approximately twice as great in the maintenance groups of either 5 or 10 mg/kg administered every eight weeks compared with the treatment group administered only a single 5 mg/kg dose of REMICADE. Please note, there was no true placebo group in this study.

Likewise, the unique clinical benefit of REMICADE for fistulizing Crohn's disease is shown here. Two-thirds of patients who received a three-dose induction regimen of 5 mg/kg of REMICADE at zero, two and six weeks achieved the primary endpoint of fistula response, defined as a 50 percent or greater

reduction in the number of draining fistula.

Furthermore, more than one-half of patients who received REMICADE achieved complete response, defined as absence of any draining fistulas, compared with only 13 percent of patients who received placebo.

Now REMICADE is already approved for this induction regimen, and Centocor presently has a pending supplemental biologic license application under priority review at the FDA for maintenance therapy for fistulizing Crohn's disease. Suffice it to say, for Crohn's disease, whether luminal or fistulizing, REMICADE provides an important clinical benefit, and fulfills an unmet medical need.

In conclusion, REMICADE is highly efficacious for patients with rheumatoid arthritis, luminal Crohn's disease and fistulizing Crohn's disease, and these are patients who have failed conventional therapies.

Treatment related serious adverse events do occur with REMICADE use, but they are infrequent. Centocor remains committed to continue to characterize

the safety profile of REMICADE and implement further risk management initiatives as needed.

We also look forward to the FDA Arthritis Advisory Committee's and FDA's deliberation, assessment and guidance with regard to the known but, more importantly, potential risks of anti-TNF agents.

We believe the benefit to risk profile for REMICADE for both rheumatoid arthritis and Crohn's disease continues to be excellent.

I'd like to thank you for your attention, and Centocor and its consultants will now be happy to answer any of your questions.

CHAIRMAN ABRAMSON: Thank you very much. May I ask first a question regarding dose. Is there any difference between the 3 mg/kg and higher doses with regard to either the opportunistic infection or the lymphoma reports?

DR. SCHAIBLE: Well, you saw the individual cases for lymphoma in clinical trials, and the range there was the lowest dose we have ever studied, which was 1 mg as a single infusion up to several doses of 10 mg/kg. So, certainly, for

lymphoma there has been no relationship to overall drug exposure.

With regard to opportunistic infections, in our clinical trials we have not seen -- We don't have that many opportunistic infections in clinical trials, and haven't seen a dose relationship there either.

CHAIRMAN ABRAMSON: Other questions? Dr. Gibofsky?

DR. GIBOFSKY: It's been suggested by several speakers today that we ought to be cognizant of the effect of prior concurrent DMARD immunosuppressant therapy on the subsequent development of lymphoma.

I am intrigued by the data that you showed in slides 8 and 9 showing that in the placebo groups, presumably matched for DMARD use and other variables, there were no cases of lymphoma development. It was only seen in the populations taking REMICADE.

To what extent does that discount, if you will, the dispositiveness of prior concurrent immunosuppressive or DMARD therapy in the development

of lymphoma?

DR. SCHAIBLE: I think, as Dr. Boscia touched on in his presentation, if you look at the absolute placebo exposure in our studies, it's less than 20 percent compared to the overall REMICADE exposure. So I think a major interpretive problem occurs by the large discrepancy in exposure between REMICADE and placebo treated groups.

So it's very difficult to interpret that data or to evaluate the point that you've raised.

DR. KROOK: A follow-up on that question: Are those people on the placebo arm now receiving REMICADE? Is that the reason for the small number, that they have crossed over? In other words, the number that's in the placebo will really not change over time greatly.

DR. SCHAIBLE: That's correct. That's actually static right now, because most of those patients do cross over ultimately, and they are censored at the point of time that they cross over.

DR. KROOK: So in these groups, as they are listed here, actually, the placebo group is almost

at its maximum?

DR. SCHAIBLE: It will --

DR. KROOK; It will increase some.

DR. SCHAIBLE; It will increase minimally, because those patients are followed through five years after their initial treatment in the clinical trial, but it will be minimally.

DR. KROOK: But they have been crossed over, if I'm right?

DR. BOSCIA: Right. It's much worse in the Crohn's disease population than in the RA population, because, of course, there are other therapies to treat patients with rheumatoid arthritis. For Crohn's disease, you saw our -- We don't have much placebo follow-up. There's nothing else for those patients to use. So --

DR. KROOK: Well, I would suspect also in this group, as you see the effect and as a clinician, you will cross them over when supposedly the study is done. I mean, that's what most clinicians would do.

DR. SCHAIBLE: I agree. Yes.

CHAIRMAN ABRAMSON: A question that may be

best directed to Dr. Wolfe, and he may not have the information. But the issue of having a comparable patient cohort, obviously, has been raised several times, and the Leflunomide treated patients would be of some interest, because they typically have similar indications -- that is,people who are failing to respond to methotrexate over the last several years.

I'm wondering, Fred, if you looked at that cohort as a comparator with malignancy.

DR. BOSCIA: Hey, Fred, I think that microphone will work right in front of you. There were 58 patients treated with Leflunomide in the --

DR. WOLFE: Actually,I have not officially looked at it. It's part of the group which was classified as no therapy. So within that group the rates seem to be somewhat lower, but there is -- To some extent, it depends on how you define exposure in that group as a whole, and we didn't -- We took the entire time in the data bank as the exposure rather than a specific time on Leflunomide.

So I can't comment at this moment on the Leflunomide, but the data are available.

DR. BOSCIA: I misspoke. When I said 58 patients, I was thinking of Teneret, not Leflunomide.

CHAIRMAN ABRAMSON: Dr. Day?

DR. DAY: Concerning risk management, you mentioned that REMICADE is prescribed primarily by sub-specialists, namely those who are best able to determine the benefit risk profile. Do you have any ballpark numbers of the percentage of prescribers who fall into that category?

DR. SCHAIBLE: It's over 90 percent

DR. DAY: Thank you.

CHAIRMAN ABRAMSON: Yes, Dr. Anderson?

DR. ANDERSON; I have a question also for Dr. Wolfe relating to the registry data, national data bank on slide 15. I was wondering about the comparability of the patient populations on the different drugs, whether differences in demographics and maybe reimbursement and other things would affect whether certain patients take -- which drug patients take, and what impact taking that into account might have on the results.

DR. WOLFE: Well, the REMICADE patients

are slightly older, but that would be reflected in the risk from the -- as adjusted from the SEER database. There are independent risks associated with age, with sex, and with education, and those are the effects that we could see at this time. Any other information on that? Okay.

CHAIRMAN ABRAMSON: Dr. Manzi?

DR. MANZI: I would like to just make a general comment and then a question. But I think that there is a tremendous amount of data that could be mined form these large registries that have comparator populations, which is something we are all saying that we need.

When I look at what the advantages would be, certainly, the number of patients that are in these registries is tremendous. I mean 18,000. Secondly, it represents, I think, more of what the general use of these drugs are than possibly the artificial environment of clinical trials, although you get important information from those as well.

I guess, lastly, it is certainly an advantage over passive surveillance and counting on

people just reporting. So I would have a lot of questions for the owners of these registries that might help us, because I think that information may be there that a lot of us need.

So my question to our chair is: Do you think this afternoon would be the appropriate time to have a dialogue with people that have these registries in Europe and here as to how much information we could get now from them that may be helpful?

CHAIRMAN ABRAMSON: I think that's important and, in fact, one of the questions is how we should go forward in capturing information. So existing and novel ways to do that, I think, is an important part of the discussion. Dr. Jaffe?

DR. JAFFE: One issue that hasn't been brought out is sort of the change in diagnostic criteria for the diagnosis of lymphoma over time. When I started in hematopathology 30 years ago, a lot of what we call lymphoma today was pseudo-lymphoma or atypical hyperplasia in the patient with rheumatoid arthritis.

So I was just wondering with respect to

some of the registry data whether that is reflected by an increase in incidence in lymphoma over time due to change in diagnostic criteria that may not be real?

DR. WOLFE: I'm afraid I have no information on change in diagnosis over time. The registry -- If you recall it, REMICADE has only been out for about four years. I am not sure that there would be any change in diagnosis, except that the rate in the SEER data banks has been increasing, and this reflects the rate that everyone else used up to now.

DR. JAFFE: Well, I think it's just a caution that, if you are going to use historical data to compare incidence figures, you have to be careful as to what the diagnostic criteria were used.

CHAIRMAN ABRAMSON: Especially in concepts of regression and the notion of pseudo-lymphoma and Sjogren's and what-not.

So we thank you very much. We are going to change the agenda slightly. We are going to break for lunch now and have the open public hearing when we return at 2:00 p.m. So thank you very much.

(Whereupon, the foregoing matter went off the record at 1:11 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:09 p.m)

CHAIRMAN ABRAMSON: We would like to begin the afternoon session. So can people please take their seats.

We are going to begin the session this afternoon with the open public hearing, and we have four -- five individuals who would like to speak, and our first guest is Mr. Rodger deRose who is President and Chief Executive Officer of the Crohn's and Colitis Foundation of America. Mr. deRose.

MR. deROSE: Thank you, Mr. Chairman, and I would like to thank the committee for giving us the opportunity to share our thoughts. I know that I submitted a paper to you several weeks ago, and I don't want to read that to you. I'll just give you an executive summary of that, and then would like to introduce Rachel Hettich, one of the Crohn's patients that we have had some association with over the years.

First of all, let me say that I don't come from the medical or scientific community like many of you do, but I did stay at a Holiday Inn recently. So

I guess that qualifies me. No, I personally come out of the private sector and retired about 18 months ago to join the nonprofit world and try to leverage my business skills to help them manage their business more effectively.

The CCFA, Crohn's and Colitis Foundation of America, has been in existence since 1967. We have raised over $200 million during that time and put that into mission critical programs such as research, education, and support, and we really believe that we are one of the voices of the million or so Americans that suffer from Crohn's and colitis.

As you know, these are chronic intestinal diseases that share common symptoms. They are referred to as inflammatory bowel disease or IBD for short. I am really appearing before this committee, because one of the medications under discussion is the first therapy to receive your approval, the FDA approval, for the treatment of Crohn's disease, and the drug, of course, is what you heard earlier, infliximab, REMICADE marketed by Centocor.

At this point, I want to note for all of

you, just so that you are aware of the arrangements that we face and we have with Centocor, is that they do sponsor some of our education and awareness programs. In 2002, of the $22 million in revenue that we generated, they contributed about three-tenths of one percent or about $152,000.

The majority of our dollars come from the patient community and major donors, and in 2003 we are projecting that the contribution from Centocor will probably be in the three-tenths of one percent as well, and our revenues are expected to grow to about $26 million this year.

I also want to mention that we do have currently a co-branding commercial on air right now with Centocor, and I want to make it very clear to you that this is not an endorsement. From our point of view, this is a way in which the Crohn's and Colitis Foundation of America can add additional information to the patient community, because when they call in to the fulfillment number, they get in that packet additional information about the CCFA as well as all medications, treatments, therapies, about the disease,

talking about all drugs.

So I look at it as total patient care in terms of information and knowledge. I think, as you look at our patient community, they probably are one of the most knowledgeable with regard to this disease as well as the medications and therapies that are available to them.

One of CCFA's most important roles, we feel, is to provide our patient community with accurate and up-to-date and unbiased information about the treatment options that they have. If you look at all of our literature, you will clearly see that.

The statement that I am making today and the one that I submitted is one that has been approved by our National Scientific Advisory Committee, which is made up of some of the thought leaders, certainly, in the industry, in the field of IBD.

I want to mention that Crohn's and colitis as a disease, if you are not familiar with it, is -- It's a life altering disease, and it's notoriously difficult to deal with and treat, and the symptoms include significant abdominal pain, severe diarrhea,

sometimes patients that have to use the restroom 15 to 20 times a day, fever, and malnutrition. It's not unusual to see an 18-year-old that looks like he or she is 12 years old, because they can't get the nutrition into their body.

Over time, we know that there are other symptoms that occur, such as they become higher risk candidates for colorectal cancer, can lead to liver disease and arthritis as well. And as yet there is no cure, and it is oftentimes that Crohn's patients need to have surgery.

As I have crossed the country talking to patients, one of the patients that I've talked to that had the most in surgeries had 23, and it's not uncommon for a Crohn's patient to at least have one surgery in their lifetime, and still it's common for the disease to reoccur.

Now there are a wide spectrum of IBD patients. So their therapy must be tailored to the individual, and we recognize, as many of you do, that infliximab is a very powerful drug. We know that, and that it is only for patients with moderate to severe

Crohn's disease who don't respond to conventional therapy.

It is also indicated, as you saw, for patients that have fistulas, which is a very painful complication as well. But when administered to the right patient by an experienced physician, it can mean the difference between constant suffering and at least an active, healthy lifestyle and a productive lifestyle.

I think, if patients are properly selected, the benefits certainly outweigh the potential risks.

Now it's important to note, and I know that all of you are aware of this as professionals in your field, that infliximab doesn't work -- doesn't always work for every patient and doesn't fit every profile. However, we are greatly encouraged by some of the additional new medications that are coming to the field, and I know you were talking about some of them this morning that are currently in the pipeline, and many of these being biologic therapies that we are anxious to see come to market.

We must emphasize that, like all of you in this room, that we as the patient community, as a patient advocacy group, believe that patient safety must never be compromised. All therapies, from those that are currently on the market as well as those that are being fast tracked, need to continue to be researched for efficacy and safety, and we know that you have stringent procedures in place to do that.

So at a high level, that is where the Crohn's and Colitis Foundation stands on this. I thought it would be very interesting for you to hear from a patient that was diagnosed with Crohn's at the age of eight. Rachel is 18 now, and she has been on REMICADE for three years. Rachel.

MS. HETTICH: My name is Rachel Hettich. I am 18 years old, and I have Crohn's disease. I was diagnosed when I was eight years old. I had just started the third grade and began to have constant stomach pains. I lost weight very rapidly and noticed a decrease in my energy.

At first, I was able to keep up in school, but things just kept getting worse and worse. The

pain from my stomach aches was excruciating and very draining, both emotionally and physically. Dealing with it 24 hours a day was very frustrating.

Basically, it shut down my life for long periods of time. Just making it through a whole week of school was a huge accomplishment. I don't really remember it now, but my parents tell me that most of the summer I was curled up on the edge of the couch in pain for hours and even days at a time. My whole life would just shut down, and so would my family's.

To control the severity of my disease, my doctor tried a variety of medications and treatments, including Asacol, Pentasa, 6-MP, MG-2 feedings, central IV lines, and even several surgeries. Finally, after much consideration, my doctor recommended trying REMICADE.

My first treatment was three years ago when I was a sophomore. We knew there might be some risk with REMICADE, but we really had no other choice. Living with Crohn's disease is like crossing a raging river by walking across on logs. You put your foot out and just hope that there will be another log to

step onto.

When they finally put me on REMICADE, the difference was like night and day. I was back in school and acting more like myself. I gained back my energy and weight as well as a healthier appearance. I could eat just about anything, which was a major deal for me. It was wonderful.

It only takes a few days after my REMICADE infusions for me to begin feeling better. It's like a switch that gets flipped on.

On behalf of all people who suffer with IBD, I would like to express sincere appreciation to all the researchers who work so hard to improve the quality of our lives. I look forward to the future with great anticipation of medical breakthroughs that may not only treat the symptoms of IBD but perhaps even cure the disease. Thank you.

CHAIRMAN ABRAMSON: Thank you, Rachel. The next speaker is Ms. Timms-Ford.

MS. TIMMS-FORD: Good afternoon. My name is Betty Timms-Ford. I'm from Denver, Colorado, and I am here today representing myself, although my travel

expenses to attend this advisory committee meeting are being paid by Abbott Laboratories.

I'm here today to share my experience with rheumatoid arthritis and HUMIRA, a medication that has greatly improved my RA and given me back the active life I had before RA took over my day to day existence.

In April 1990, as a 48-year-old woman, I noticed swelling and redness in my knuckles, and at the same time started experiencing some pain. I visited an internal medicine doctor who initially diagnosed rheumatoid arthritis but referred me to an arthritis specialist who, after various tests, confirmed that I did indeed have RA.

My doctor initially prescribed mild medications which seemed to have little effect in relieving my pain and swelling, and my RA continued to worsen. He referred me to a physical therapy clinic where they started me on various exercises in an attempt to keep my joints mobile.

They gave me adaptors for my car keys, toothbrush, and even pens and pencils, as I was unable

to close my hands enough to grip these items without aids. At this point, my day to day existence consisted of rising, preparing myself for work, working an eight-hour day, coming home, climbing the stairs and going straight to bed.

At my desk at work, the pain in my feet was so severe at times that I used a pillow on the floor as a cushion for my feet. Rising from most any chair at home required my husband's assistance, and on days I felt good enough to grocery shop, I would use the shopping cart to steady myself and wrap my arm around items on the shelf and drop them into the cart.

My doctor tried numerous medications, hoping to find the right one for me. My RA did improve, but I was never able to completely recapture the energy level I had before developing RA. That is, not until I started in the HUMIRA drug study program in August of 2000.

I never gave up on incorporating some exercise routine in my lifestyle, but since starting HUMIRA, it is very rare that I experience any pain, and I am now, weather permitting, walking two to three

miles most days on my lunch hour, and three or four nights each week after working eight or nine hours, I head straight to the gym and work out for one, one and a half hours.

If an occasion arises, I tell people I have RA. Their response is almost always, I never would have guessed; you certainly don't exhibit any signs of arthritis.

I also have been able to involve myself in a lot of volunteer work that I was doing previously until my energy level was drained so severely. I consider myself extremely fortunate that I was blessed with an inordinate amount of energy and also found a wonderful doctor who was willing to involve ;me in the HUMIRA study program.

HUMIRA has had a tremendous impact on my life, and I appreciate the opportunity the committee has given me to share my story during your meeting, as I think it is important for others to know how invaluable this drug has been for me and, undoubtedly, would be for others suffering from RA.

Thank you for your time and attention.

CHAIRMAN ABRAMSON: Thank you very much. Lucille Cerretta.

MS. CERRETTA: Hello. Thank you for having me today. My name is Lucille Ann Cerretta, and I'm here to share my personal experience with rheumatoid arthritis and HUMIRA.

Abbott Laboratories has provided my travel so that I could attend this meeting.

I am a 50-year-old woman, and I was diagnosed with RA when I was 37. I have been on a host of drugs over the years, including prednisone for more than a decade. None of these treatments had the results of HUMIRA, and some almost took my life.

Not only did I have to fight the pain of RA, I had to live with the side effects of those medications. I am finally off those drugs, thanks to HUMIRA.

The pain and suffering I had to ensure are really hard to capture as I stand here and speak to you. I was unable to work, and had to live on disability. That alone is a challenge. Try living on $500 a month.

I turned to art to ease my pain. I used modified brushes that were built up so I could hold them. I would go to Home Depot and buy tubing that was about this big, and I would start to paint.

Today, with HUMIRA, I am exhibiting my artwork, standing at exhibits, carting paintings in and out of my van, and carrying them into galleries. I'm in two galleries right now that are upstairs lofts. So I have to carry my paintings up the steps, and I do it.

Not only do I feel better, but I am no longer using a cane, looking at scooters to buy or sleeping with a brace. I also appears that I have had improvement or reversal in some of the damage done. I am now down to wearing one brace on my fingers, where before I needed four.

I have experienced a hard life, but I am a positive person and always believed research would someday find an answer to this crippling disease. I only wish I was just now being diagnosed. Today people with RA have the option with HUMIRA that allows you to continue living the life you already have. I

didn't have that option until two years ago.

I am so grateful that RA patients now have a treatment like HUMIRA. Without it, myself and RA patients like me would revert back to being dependent on others, and nobody wants to do that.

Thank you for allowing me to share my story with you today. I really appreciate it. Thank you.

CHAIRMAN ABRAMSON: Thank you very much. Judy Levinson.

MS. LEVINSON: Good afternoon, Mr. Chairman and members of the Food and Drug Administration. My name is Judith Levinson. I am a 58-year-old individual who has suffered with rheumatoid arthritis for 18 years. I have been on the drug Enbrel since January 7, 1999.

Since that time, I have administered approximately 431 shots. I am not a paid spokesperson, but I do own Amgen stock. I purchased it two weeks after I began my treatment, because I had such confidence and trust in this drug and this company.

Some of you might remember me from April 11, 2000, when I asked for your approval for newly diagnosed patients to have the opportunity to receive Enbrel as part of their treatment. I applaud you for making that possible.

On August 17, 2001, I spoke to you regarding safety of Enbrel. These ongoing reviews of new biologic modifiers is essential to protect all individuals from potential harmful side effects.

One recommendation was for doctors to encourage their patients to be tested for TB. I took that advice, and my TB test was negative. Enbrel patients are also advised by the inclusion of information packets in the dosing boxes to immediately notify their physicians about any serious infection they may experience.

I told you about my 14 surgeries I have undergone to correct hand, wrist and foot deformities caused by severe RA. Over the past 18 years I have taken many prescribed drugs, some of which have caused serious side effects, including nausea, fluid retention, puffiness, stomach distress, and headaches.

I'm happy to say that on Enbrel I have experienced none of these problems nor have I had any infections, not even a single cold. Every two months I undergo complete blood panels to evaluate the status of my health to ensure that I am remaining within the parameters of normal levels.

Amgen is diligent with respect to keeping their users informed about any findings regarding Enbrel. I have every confidence that Enbrel is safe and that, if any problems should arise, I will be notified immediately to contact my doctor.

Approximately 100,000 people now benefit from this incredible drug. To me, Enbrel has been a miracle. It has given me back my life. Before taking Enbrel, I visualized myself requiring assistance even to do the simplest of tasks, but not now.

Today I am a productive individual, a wife, a mother, a daughter, and a sister. I'm a published poet and a fused glass artist. Around my neck I am wearing my signature piece, a wounded dove, made from small bits of glass that I designed with these hands. Enbrel has restored my strength,

stamina, and allowed me to forgo my afternoon naps, giving me a better quality of life than I ever thought was possible.

My husband calls me his energized bunny, because I am always in the go mode. I am always amazed by people I meet who either know someone using Enbrel or want to know about the benefits of this drug.

Last week, I met someone whose brother has RA and is being treated with bi-weekly injections, and she said that he has been given a second chance to life.

The safety of all drugs is extremely important, and it is very reassuring to know that you, the FDA, considers it such a high priority. I'd like to thank you allowing me to speak to you today.

CHAIRMAN ABRAMSON: Thank you. We thank each of the speakers. I think it is so important for us. The courage that you all show is -- we need to be mindful of that, and because our charge is to look at the benefit and the risks of these medications, and I think hearing a person's story can bring home to us as

physicians and others the details of this condition that we can't read particularly in the papers and the dossiers.

We have one more public statement to be read in by Ms. Reedy from Colleen Andrus.

MS. REEDY: Colleen Andrus writes: "I am currently a patient with rheumatoid arthritis and am on a regimen of Enbrel and Arava. My attending physician is Dr. Michael Schiff at the Denver Arthritis Clinic.

"I understand that Enbrel is set for review and evaluation this year, and am writing in support of this wonderful medication. I am 54 years old, and was diagnosed with RA about five years ago. Treatment has involved several different RA drugs prior to Enbrel, all of which were eliminated for my treatment, either because they did not relieve symptoms or I had some type of adverse reaction.

"I began injections of Enbrel in July of 2001, and my quality of life has improved significantly. I have had no side effects, nor site reactions. It is quite reassuring to know that there

is treatment upon which I can depend, and that I can continue a fairly normal lifestyle. I have always been very active, and the problems with RA have been challenging.

"Although I have not yet experienced any serious joint deterioration, I found that fatigue and moderate to fairly severe joint pain was constant without Enbrel. My grandmother suffered form severe debilitation from RA, and, of course, I am concerned that my condition will progress. To date, I am happy to report that my current treatment seems to be very successful, and progress of the disease seems to be inhibited by my current drug regimen."

Her next paragraph addresses the difficulty in opening the vials and in piercing the caps with hypodermic needles. Take note. She closes:

"I hope that Enbrel will continue to be approved by your agency, as having a choice of treatments is very valuable to those of us with RA."

CHAIRMAN ABRAMSON: Thank you. We are now going to enter the segment of addressing the questions put to the committee, and Dr. Siegel will introduce

the questions. Then I think what we will do is the panel will have a discussion of each of -- There are six questions pertaining to lymphoma. As we go through each one, the panel will make their comments, and then if any of the sponsors would like to make a comment after we discuss a point, you are welcome to sort of come to a microphone and make a statement or a clarification.

So, Jeffrey, would you like to begin, please.

DR. SIEGEL: Thank you. I want to make a few concluding remarks, and then discuss the questions that we wanted to pose to the committee.

Before we begin, I wanted to just review some of the data for lymphomas. We have asked the panel to concentrate particularly on several different adverse events, and we have presented a lot of data over the course of the morning. So I thought it would be helpful to just review some of the key data.

We have presented two different analyses for you for each of the products. One is an analysis of the controlled portions of the controlled trials

where we think the experience is comparable between drug and placebo. Separately, we have presented data from the overall database, including the standardized incidence ratios.

For adalimumab in the controlled portions of the clinical trials, two cases of lymphoma were observed among 1380 patients who saw a mean exposure of 0.6 years. In the placebo control arms of these trials, zero cases of lymphoma were observed among 690 patients with 0.5 years mean exposure.

In the overall safety database for adalimumab, ten cases of lymphoma were observed among 2400 patients. This was over a course of 2.4 years median exposure, and a calculated standardized incidence ratio of 5.42 was calculated with confidence intervals as shown on this slide.

By the way, all of the data that I am going to be showing you in these first slides is in your handouts, but these slides are new, just to place it in summary form.

For etanercept, one case of lymphoma was observed in the controlled portions of the clinical

trials in the etanercept arm, among 2502 patients receiving a mean exposure of 0.5 years.

In the placebo arms of these trials, no cases of lymphoma were observed among 921 patients with a mean exposure of 0.5 years.

In the overall etanercept database, six cases of lymphoma were observed among 3389 patients receiving a mean exposure of 2.2 years. The standardized ratio here for the total database was 2.31, with the confidence intervals as shown on the slide that do overlap one, 0.85 to 5.03.

Finally, for infliximab, in the controlled portions of the clinical trials, three cases of lymphoma were seen among infliximab treated patients, among 2421 patients who received a mean exposure of one year.

In the placebo control arms of those same studies, there were no cases of lymphoma among 489 patients with a mean exposure that was similar to the infliximab group of 0.9 years.

In the overall safety database for infliximab, six cases of lymphoma were seen among 2421

patients receiving a mean exposure of 1.7 years. The standardized incidence ratio here for the infliximab database was 6.98 with the confidence intervals that exclude one, namely from the lower bound of 2.56 to 15.19.

So in summary, the newer data that we have presented show an occurrence of lymphomas with each of the approved TNF blocking agents. In controlled trials, we see one to three cases of lymphoma with the study drugs versus none with placebo.

In the controlled plus the non-controlled extension trials, we saw a higher rate of lymphomas than observed in the general U.S. population, based on comparison to the SEER database, and additional cases of lymphoma have been observed in the post-marketing experience.

It is important to keep in mind, as you have heard several times over the course of the morning, that higher reported rates of lymphoma have been observed in RA patients, and this clearly complicates the analysis.

In terms of congestive heart failure, the

data you've seen this morning suggested deleterious effects of infliximab in congestive heart failure patients, and data from the etanercept trials showed some concern in trends in congestive heart failure patients receiving etanercept.

We don't know what the effects of adalimumab are on similar congestive heart failure patients, because studies are unavailable.

So in conclusion, the approved TNF blockers are associated with high ACR response rates in rheumatoid arthritis and beneficial effects for progression of structural damage.

For infliximab, there is also an additional prove claim of improvement in physical function as based on the Health Assessment Questionnaire, based on data from a long term study. Data for this same improvement in physical function are currently being collected for the other TNF blockers.

A number of serious but uncommon adverse events are also associated with the use of TNF blockers, and for some adverse events these risks can

be reduced with appropriate screening.

Turning to risk management, it is, of course, important to maximize the benefit of treatment with these agents and to minimize the risks associated with their use. For the identified risks of TNF blockers, it is important to collect data to accurately assess this risk, to minimize those risks where appropriate by patient selection and screening, and by appropriate risk communication.

So finally, the agency welcomes discussion on the part of the Advisory Committee regarding lymphoma of the confounding factors in assessing causal relationships, in the Advisory Committee's assessment of the likelihood of causal relationships between lymphomas and TNF blocking agents.

We welcome their advice on how to collect data that would help assess causal relationships, and on selection of appropriate language for package labels to communicate the available information.

Regarding congestive heart failure, we welcome discussion of approaches to risk management. Thank you very much.

CHAIRMAN ABRAMSON: Thank you. What I will do is read the first question and then open it for discussion to the panel members.

Question Number 1: Please comment on the characteristics of the cases of lymphomas -- that is, age at time of diagnosis, distribution of non-Hodgkin's lymphoma versus Hodgkin's disease, histology, etcetera -- observed in patients treated with TNF inhibitors relative to the experience in the general population and relative to the experience in people with underlying rheumatoid arthritis or Crohn's disease.

What I'd like to do to begin is that we have three experts, particularly in the field of oncology and lymphoma, Dr. Blayney, Krook, and Jaffe, and I would ask first to solicit their opinions. Then we can open up for more extended discussion. Dr. Jaffe?

DR. JAFFE: With respect to the first question, I think, unfortunately, we don't have a lot of the data that we really need to answer this question. I think most of the lymphomas that have

been reported in the session today and in the literature have not been adequately studied so that we can draw definitive conclusions. But I think, based on the data available, I would say that the pattern of lymphoma occurrence is similar to what one observes in rheumatoid arthritis and less similar to what one sees in the general population.

In general, the proportion of non-Hodgkin's lymphoma to Hodgkin's disease tends to be somewhat higher, as it is in the rheumatoid arthritis patient population, and the overall incidence of follicular lymphoma, the most common lymphoma subtype in the United States, is relatively low.

So I think, from my perspective based on the data, it resembles the pattern of lymphoma that you see in rheumatoid arthritis.

With Crohn's disease, those cases have not been extensively studied. There are small incidences of lymphomas associated with immunosuppression, and those are sometimes Hodgkin's and Hodgkin's-like lymphomas as well as large cell lymphomas.

CHAIRMAN ABRAMSON: So from a pathological

perspective, the issue had raised whether patients with immunosuppression develop a certain kind of lymphoma. Are you also saying that this is not the kind of lymphoma that these people are developing?

DR. JAFFE: No. I think some of the lymphomas that are seen in rheumatoid arthritis are related to the other therapies that are used, in addition to the underlying disease. So I think we have two confounding variables when trying to look at these particular drugs that we are considering today.

One is the other agents such as methotrexate and to the lymphomas that occur sporadically as a consequence of the disease itself. I think the Hodgkin's and Hodgkin's-like lymphomas and large cell lymphomas are the ones that are generally related to the immunosuppression.

CHAIRMAN ABRAMSON: Thank you. Dr. Krook.

DR. KROOK: I will echo some of Dr. Jaffe's concerns. I know, as I look at all three TNF inhibitors, generally they are older patients and generally they have had a long duration of the rheumatoid arthritis.

Some of the confounding things are, just as Dr. Jaffe said, how long the other drugs which have been involved and where it is. Now one of the other things that in some of the documents which I received there were some of the follow-up on this. If I remember right, there were not very many deaths. They were treated and did fairly well, and I think that that relates to that also.

I think that, if you look at the incidence of Hodgkin's in the overall population, it is probably similar, one Hodgkin's or two Hodgkin's to nine or ten of the other, and I think that is very similar.

I think the other thing is that we just need to see what happens with these people, whether they act the same as others. But again, this is a heavily pre-treated group of people. My impression is that it is very similar to what one sees in the overall population.

CHAIRMAN ABRAMSON: Dr. Blayney.

DR. BLAYNEY: I'm struck by what we don't see here. As Dr. Jaffe pointed out, we don't see follicular lymphoma, and we don't see a lot of

Hodgkin's disease. What we do see is lymphoma that seems to be related to the background incidence in rheumatoid arthritis, and perhaps in these heavily pre-treated patients or these advanced disease patients, it's very difficult to sort out which is which.

There is some acceleration in the underlying propensity to develop lymphoma of the B cell, large cell type. Furthermore, we don't see Kaposi's sarcoma, and we don't see an excess of melanoma. Perhaps these people aren't exposed to the Kaposi's sarcoma infectious agent and aren't exposed and develop Kaposi's sarcoma. So I find that reassuring.

The third thing we don't see in the heart failure trials, or at least we didn't hear about it in the heart failure trials, was lymphoma developing in patients with heart failure who are exposed to these agents, albeit for six months to 12 months. So I find that data reassuring as to the safety of these compounds as a class.

There may be some difference among the

three that needs to be explored, but I basically am reassured by what we don't see.

CHAIRMAN ABRAMSON: Thank you. Other comments from members of the panel? Dr. Williams?

DR. WILLIAMS: As I have had the chance to review the extensive materials and listen today, I don't see that I can expect anymore incidence of lymphoma with etanercept than I would based on just the incidence we see with rheumatoid arthritis. There may be perhaps some increase with monoclonal antibodies, but even that is in patients with chronic inflammation and who have been exposed to other immunosuppressive agents, and I don't think causality can be determined at this time.

I thought the statement that was made in adalimumab's labeling was very fair in terms of notifying people what the potential was, but we need much more data before we can say it was caused by these drugs.

CHAIRMAN ABRAMSON: Other comments?

DR. MAKUCH: Just a few comments, one of them being: I think, actually, that the SIRs are

actually perhaps even more comparable than what was just given in the summary, as I know that for Enbrel the one given to us was 2.3, but on the other hand, I think there is some going back and forth on whether it really is six or nine cases, in which case for nine cases then you do have a significant SIR of 3.47.

So it seems as if one of the things I wanted to make a comment about is, I guess -- or raise, is the issue about a class effect versus individual drug effect. When I do look at, especially with the Enbrel alternative, SIR 3.47, they all seem to coincide with one another.

The second comment was, I guess, looking at it a different way but sharing the remarks of everyone else up to this point, we really didn't see information about concomitant meds. We really didn't see, despite numerous questions earlier, about duration of treatment or dose, other prognostic features.

So it really then is very difficult to separate out the underlying association between the lymphoma cases in RA versus the lymphoma cases with

respect to it being due to these drugs.

I think the final remark is regarding the length of follow-up. I did hear the entire morning that the risk is constant over time and, if you do believe that the risk is constant over time, then I think the data that we see are fine.

If you do not believe that the risk is constant over time, and looking at some things, I think it might not be -- it may increase over time. If that's the case, then what we may be seeing would be then an underestimate of the risk associated with these compounds in their relationship to lymphoma.

So I guess the summary comment is just some of the things that we did not see are actually fairly uniform SIRs among the three, indicating at least some discussion about a class effect, and finally the effect of length of follow-up on the true risk if you do not believe that the risk is constant.

CHAIRMAN ABRAMSON: So if we can go back just to the first point number one question on the histopathology, is it fair to say that, in summary, the kinds of lymphomas we are seeing are consistent

with those that we have seen in the past in rheumatoid arthritis patients, which differ a little bit from the normal population where you see more follicular cell. So, therefore -- and there is nothing distinctive that we are seeing that says it's a third class, a different kind of tumor that might be peculiar to this class such as we see in HIV or what-not.

So it's consistent with the disease historically. Is that a fair summary? What we have observed in the disease in the past --

DR. JAFFE: What we have observed in the disease, both sporadically and with given therapies; in other words, I think that some of what we see is related to other therapies that are used for the disease.

CHAIRMAN ABRAMSON: Right. So without ascribing causality, it's just the histopathology is consistent with RA and treated RA.

Any other comments on the point one from the committee members? Yes?

DR. ILOWITE: Mostly a question. There was some discussion about EBV histology, EBV genome in

the tumors. Would that be helpful in elucidating this issue?

DR. JAFFE: No, I think those are the data we need. I mean, I think that the sporadically occurring lymphomas that you see in rheumatoid arthritis and those associated with therapy are often EBV positive, particularly those occurring in patients related to therapy, methotrexate and other immunosuppressive agents.

CHAIRMAN ABRAMSON: Are there comments from any of the sponsors with regard to this first question? Dr. Siegel, anything more on point number one before we go on? Okay.

All right. So question number 2, I'll read again: Please discuss the strength of the available evidence, including the pre-marketing controlled trial experience, open label extension studies, post-marketing registry data, and post-marketing spontaneous reports, incidence rates over time, etcetera, and any conclusions you are able to draw regarding an association between TNF-blocking treatments and lymphoma.

Once again, I think I will begin the discussion with some of our experts in this area perhaps, and that is Doctors Day, Elashoff, Makuch and Anderson in terms of epidemiology and biostatistics. Then we will open it up to other members of the committee. Dr. Day?

DR. DAY: I have no comment.

CHAIRMAN ABRAMSON: Dr. Elashoff.

DR. ELASHOFF: Yes. To assess how either reassured or disturbed we should be by what we see in terms of the lymphoma SIRs, I would need some additional biologic medical information. What is known or believed about how long -- what the latency is from the time of some triggering event to diagnosis of lymphoma.

If we were to conclude that these drugs were affecting it, would we be thinking it was triggering the initial development or perhaps stimulating things? So if we think it is perhaps triggering it, have any of these follow-ups really been long enough so that we would expect to see anything yet?

So I would need some discussion of that point in order to assess the data we have.

CHAIRMAN ABRAMSON: Dr. Makuch.

DR. MAKUCH: I think, very briefly, the strength of the available evidence -- I think there are some issues. One of them is just very small numbers. Just a few cases one way or another would make a substantial difference. I think that any kind of analysis in which you did vary this, sometimes called sensitivity analyses, may lead to substantively different conclusions.

So, therefore, the strength of the available evidence, to me, is not overly strong.

I did mention as a second general category about evaluating the evidence, concomitant meds, duration of treatment, dose, prognostic features, etcetera. Without having more information about that, one cannot reliably understand the extent or nature of the association to any great degree.

Finally, again getting at the constant risk -- and again I think Dr. Elashoff said the same thing in a slightly different way of looking at the

length of follow-up. I really would have a much higher comfort level with seeing data six months or a year from now in which the length of follow-up is longer, and again because the -- If you do not believe that the risk is constant over time, there may be an issue there.

I would have liked all of the sponsors probably to have done one additional analysis, which is called a hazard analysis, which is an explicit evaluation of the risk question *per se*, which was not done here.

CHAIRMAN ABRAMSON: Dr. Anderson.

DR. ANDERSON: I don't really have anything to add to what Doctors Elashoff and Makuch have said.

CHAIRMAN ABRAMSON: Are there other comments people think the strength of the evidence -- Oh, okay, Dr. Krook.

DR. KROOK: I think, as we look at this, and the question is that the committee or whoever follows this is going to have real problems, because you have three drugs here which are going to be used

fairly extensively in the community, and I think that is going to confound things unless we have an older control. But then we have problems with timing, all the other things that were talked about, geography and otherwise.

My own looking at this, the pre-marketing controlled trial is probably almost as good as we are going to do and see what happens with these people. Unfortunately, I heard that most of the placebo group has crossed over, and that's going to be a problem, because I think you are going to see with that one even -- you are going to perhaps see a few more lymphomas, as somebody said, down the line. One or two more lymphomas are going to change the whole thing. We are going to get away from the SIR. We are going to get outside the confidence limits.

So I'm not sure we can do much better than we are now. The other comment which is interesting on post-marketing is I was impressed by the national database that most of the adverse events were coming from patients, not from physicians and whatever, although -- and that adds to the problem.

CHAIRMAN ABRAMSON: Yes, Dr. Unger?

DR. UNGER: I have a comment about one of Dr. Fischkoff's slides with respect to the risk of lymphoma over time. I don't know if there is any way we could see one of those slides or you could look in your packet, slide 43.

Dr. Fischkoff presented this slide, and his interpretation was that the risk was, in fact, constant over time. In my examination of the slide, I arrived at a different conclusion, which is that I see -- between day 620 and 840 approximately, I see five out of ten of the cases of lymphoma in a 200 day period.

Now I'm not a statistician, but you have 2000 days of follow-up. You have ten events. So if this were sporadic, one would expect one event per 200 day period, and we are looking at five events in that period of time. I'm wondering if anyone else made that observation and if there are any comments about that.

DR. MAKUCH: Which slide number are you talking about?

DR. UNGER: That slide. It's slide 43. I mean, the way the scale is drawn, it's hard -- Aha. I have a pointer. In this area right here, there are five events, and they occur 21 to 28 months after initial exposure.

A related question that I have -- it's a rather provocative question, but being that we have some epidemiologists here: If one does something to cause cancer, if one blows up a nuclear device or you have a Chernobyl and there's a bump in lymphomas, what is the lag time?

CHAIRMAN ABRAMSON: Dr. Blayney, would you like to address that? Dr. Blayney or Krook?

DR. BLAYNEY: I think there's several answers to that question. One, we are not -- The cancers, as I understand them, that relate to damage from DNA from radiation exposure and, by the way, from alkylating agents probably have a peak incidence of five to six years after the treatment.

The other -- and this goes to Dr. Elashoff's question, the best models of immunosuppressed related lymphoma that I know are HIV.

So HIV, you see the lymphomas way at the tail end of the disease course when the immunosuppression is quite profound.

In this instance, it depends on where you start the clock. Do you start the clock at the diagnosis or rheumatoid arthritis and all of the other things that happen to a RA patient in that time or do you start the clock when they receive the anti-TNF agent?

My supposition would be, and my hypothesis would be to start the clock when the rheumatoid arthritis diagnosis is made. So I think maybe a year of follow-up is not going to be helpful, because that's a small percentage -- a small absolute percentage of the time course when patients are at risk for developing one of these lymphomas.

In the transplant setting where you have iatrogenic immunosuppression, I don't remember what the peak incidence is, but I think the point to your question is there are a lot of different ways that people get secondary malignancies, and here we are talking about an immunosuppressive event.

DR. WEISS: In the transplant setting the lymphoproliferative diseases that do occur tend to occur rather rapidly in the course of disease, and oftentimes, too, those might regress once you remove the immunosuppression. So they do seem to be of somewhat different character.

DR. KROOK: Just interesting. In Doug's model there, if you start at the time of the rheumatoid arthritis, you would have a curve that would certainly stretch that farther out. I suspect this is from the inhibitor.

The other thing: I think on the slide that was shown, if you can put it back up, there are some patients which are probably back at day 800 and 1000, if I'm right. So you don't have all -- if I'm correct, all 2500 patients that are 2000 days out, unless I'm wrong. They may be thinking of cancer curves, but at least usually there is a bunch coming along.

DR. BLAYNEY: But if I may respond.

CHAIRMAN ABRAMSON: Yes, go ahead.

DR. BLAYNEY: to the left of that there is

a bunch of patients who never got to this, who may have developed lymphoma from rheumatoid arthritis and didn't qualify for the treatment with the experimental agent. So this sort of -- it doesn't include -- there is a selected bias in this slide 43 against people who might have developed lymphoma from the rheumatoid -- or the underlying condition or its treatment, as Dr. Jaffe has pointed out.

CHAIRMAN ABRAMSON: Dr. Fischkoff, did you want to make a comment?

DR. FISCHKOFF: Yes, a couple of comments. Number one, the reason that we presented the data this way is because, as has been discussed here, not all patients have had equal exposure, and in order to correct for that, we thought the Kaplan-Meier analysis would be the correct one to do rather than choosing some arbitrary bins.

The other reason that we also felt that that was an appropriate analysis is because the shape of the curve that you get also depends on the selection of the bins. If you look at it by years instead of by six months, you see that there were

three in the first year, four in the second year, two in the third year and one later on, of course, recognizing that not all patients have made it that far.

So those are the two reasons for the one that you had brought up, and also because there is also some effect of the way you choose your analysis bins on the shape of the curve. It was our feeling that this analysis correct for those kinds of effects.

CHAIRMAN ABRAMSON: Yes, Dr. Makuch.

DR. MAKUCH: I agree it does actually do a nice job of showing that. I think the issue was whether or not it is consistent with constant risk or not constant risk. Actually, it took me about ten minutes for my eyes to focus on the graph, but I think I can see it now, and I would agree with you that -- because as you go through those bins in time, there are fewer people at risk.

So since all of a sudden, you are having that clumping between, let's say, 600 and 800 days with fewer people at risk, that really does indicate to me that there might be an increasing risk for some

period of time. If there is, then that figure actually argues fairly persuasively for one to two-year follow-up as being necessary to perhaps assess the full risk associated with what we are examining here.

CHAIRMAN ABRAMSON: Thank you. Dr. Gibofsky.

DR. GIBOFSKY: I share the concerns of my colleagues across the table with regard to the caveats imposed on the strengths of the data at the present time. That said, I think we have to be careful not to confuse a temporal association with a causal association. They are quite different, both scientifically and to our patients.

That said, I want to get back to Dr. Manzi's comment earlier, that if we are asking these kinds of questions, we really do need to come up with the methodology and the data to mine that will us be more precise in the answers that we want to arrive at.

I think one of our charges and one of the areas that we should be discussing is what kinds of questions we should be asking, what kind of data we

should be collecting, what kind of standard information should be required.

I was intrigued by Dr. Silman's comment that to use one of these agents in his country, there is a requirement for a national registry. Perhaps we should be moving toward some kind of effort in that regard. Dr. Wolfe has certainly taken great steps in that direction, but it would be nice if we as a group of concerned individuals and experts could prod our respective professional associations and colleagues to a similar effort.

I think that is how we are going to get a better handle and come back when we revisit this as to what information we have collected and how the data looks to us.

CHAIRMAN ABRAMSON: Exactly. And that we need to get into a little bit more as part of the next question. I guess, what is the strength of the available evidence? Obviously, the committee feels that the evidence -- there's not a lot of cases. There's some issues -- there's clear issues of numbers and the need for more data.

DR. WILLIAMS: I would like to just reiterate the comment that I think that the case, at least for etanercept, didn't make a very good case at all right now. There are no more expected than you would expect in a group of rheumatoid patients, regardless of severity of disease. So that it wasn't equal for all three groups.

CHAIRMAN ABRAMSON: Right. So this is again a question. Are they equal? On the other hand, the signals are small for each of the drugs, and it is striking that in the randomized trials you don't see much emerging in placebo. Again, not enough numbers to say causality but enough to say there might be a signal, and I'm not sure. I'm curious as to what other people think.

Dr. Williams raises the point that is this more or less for one or other of the drugs or simply can we say we have a signal emerging that needs more information going forward? I'm curious if people have comments on that.

DR. WILLIAMS: Having made the point, I would say that I would still survey all three drugs.

I would not eliminate etanercept just because it wasn't strong on that, because it has a similar effect.

CHAIRMAN ABRAMSON: Right. Okay.

DR. KROOK: Certainly, we have a time difference between the three drugs, you know. The last one in is tomorrow.

CHAIRMAN ABRAMSON: Right.

DR. GIBOFSKY: One more comment, if I might. I think we also have to focus on the dichotomy between the clinical trial and clinical practice. It was commented by one speaker that, in the context of a trial where you have wonderful inclusion and exclusion criteria, you are not always getting the real world experience. Our charge now is to come up with some recommendations for the use of these drugs for our patients in the real world.

CHAIRMAN ABRAMSON: Right, going forward. And I would like to just suggest perhaps to the FDA that there are other drugs that were approved in the same time frame, Leflunomide and Anakindra, indicated for similar kind of patient population, particularly

in the Phase III trials. It would be very interesting to go back to some of the existing databases and see what kind of signals emerge from those DMARDs.

Okay. So this is question number 2. Are there comments from any of the sponsors regarding this question 2? Yes, Dr. Boscia.

DR. BOSCIA: Hi, Jerry Boscia from Centocor. I just want to caution that you have to be careful when you compare one sponsor's product to the next sponsor's product to the next sponsor's product, because the patient populations that each company studied weren't necessarily the same.

I mean, Jeff would be the best person to comment on this, but I believe that -- and I don't know, Jeff, because I'm not privy to all the data, but some companies studied patients with early RA more so than some of the other companies studying patients with later disease, and I really think that makes a difference.

DR. SIEGEL: I think there is no doubt that that could clearly make a difference. I think the pattern that we are seeing with most of the

products that have been approved and that go through the pipeline is that sponsors initially study them in DMARD failures, in people with more longstanding active disease, and after they have shown efficacy in that population, then do a study on early rheumatoid arthritis.

That was certainly the case with etanercept, and I think we are seeing similar patterns with some of the other products. But at least early on, you will tend to see mostly data in more advanced disease, longstanding disease.

DR. WEISS: I think you also raise a good point, that it will be important as we develop more data to see more of these trials in early disease, of longer term follow-up, to -- just like the other suggestions, to be able to try to characterize the patterns of adverse events in, particularly, the lymphomas that we see, and see if they tell a compelling story.

CHAIRMAN ABRAMSON: Dr. Ilowite.

DR. ILOWITE: I just wanted to point out some issues that are uniquely pediatric. One is that

children are likely to be on these drugs, if they respond, much longer than adults, maybe 30-40 years more than similarly affected adults with analogous conditions, and that any analysis of lymphoma risk to assure safety for children would, I think, have to be longer than necessary for adults, whether there's a blip at 600 to 800 days or not.

DR. WEISS: Can I just ask. Among the slides -- We have one of the products that is right now approved for JRA, and I believe that we looked, and none of the cases occur in children with JRA. I mean, there are some young adults that have developed lymphoma, but no children. But we have asked -- I don't know; maybe Amgen can comment. There are long term registries going on in the JRA population, because it's true, it might be -- Again, they have less longstanding disease. So that may or may not be a factor.

I don't even know if there are any natural history type databases with respect to JRA to try to characterize the lymphoma rates, and I don't know if anybody has that kind of information, but I would be

very interested.

DR. BURGE: Yes. I was just going to comment. Yes, you are accurate that there have been no lymphoma cases in pediatric patients, whether in clinical trials or in post-marketing reports. Again, yes, we have initiated a registry to continue to monitor safety in kids.

CHAIRMAN ABRAMSON: Okay. Dr. Siegel, any other clarifications on this question 2?

DR. SIEGEL: No, that was a thorough discussion. Thank you.

CHAIRMAN ABRAMSON: Thank you. Question 3, Part 1: As part of post-marketing studies, all three manufacturers have committed to follow between 1000 and 2000 patients with RA and to provide the agency with updated information on malignancies annually for a minimum of five years. At five years, the agency will determine whether additional follow-up will be necessary. The yearly update includes numbers and types of tumors based on histology and other standard assessments.

Should the companies be asked to obtain

additional specific types of information not normally assessed in patient management that could help elucidate the relationship between anti-TNF therapy and lymphoma? What findings would suggest that there be continued active follow-up of this nature?

I would just open that up to members of the panel. It does also get to some of the points that Dr. Gibofsky and Manzi were talking about registries. But let's focus first on the companies' commitment over the next five years. Dr. Elashoff?

DR. ELASHOFF: Well, while studies of 1000 to 2000 patients sound pretty large and, I'm sure, are expensive to do, with respect to the kinds of rates that we think might be of concern and with respect to the total numbers of patients being treated with these drugs, those look rather small.

In addition, the five-year may be small in terms of detecting some of the kinds of things that we are concerned about.

CHAIRMAN ABRAMSON: So additional registries or patient population cohorts need to be followed in addition to that. Yes?

DR. WILLIAMS: We are still not going to have any better idea in five years what the underlying rate is for rheumatoid arthritis, regardless of stage. I don't think that data is going to get any better, because nobody will be untreated.

CHAIRMAN ABRAMSON: Right. Dr. Manzi

DR. MANZI: I guess I would echo that and just say that, to me, the only advantage of this over the current system is that you are now going from passive to more active, and you are defining a certain set of patients. But you still haven't gotten away from exactly what people have pointed out: first of all, numbers, comparator populations, and all of the other confounding issues that I think much larger registries can help us with.

CHAIRMAN ABRAMSON: Can we have a clarification as to how the 1000 to 2000 patients that are being followed have been chosen, since that is, obviously, just a subset of patients being treated with the drugs?

DR. SIEGEL: Generally, the number of 1000 to 1500 and, in some cases, some more is the follow-up

of patients who were recruited into the initial clinical trials for approvals, and then just to follow those patients along.

There was no rigorous way of deciding that this was the exact number that should be followed. So we would be open to suggestions about ways of deciding what the appropriate number might be.

CHAIRMAN ABRAMSON: So these are people in Phase III trials?

DR. SIEGEL: As these products that were being developed, we were concerned that adverse events might emerge with longer durations of exposure. So we have generally advised sponsors to, if possible, enroll patients -- to roll over patients in all the studies into active drug, so that at the time of a potential approval, we would have the largest database that could be had.

So it's the control trials but also the other trials.

CHAIRMAN ABRAMSON: Right. Perhaps I would be interested to know from each of the companies who those 1000 patients are, if they can just in 30

seconds or less describe those cohorts for us.

DR. BURGE: Yes. The patients in the etanercept long term follow-up studies are patients from initial, Phase II and Phase III studies and some additional open-label studies that were early on in the development program that those patients have rolled over into longer term extension trials.

In addition, we have another cohort from the early RA trial that's gone into open-label extension, and our colleagues at Wyeth have additionally taken the patients in their early trials in Europe and done the same thing. So those are sort of the early clinical trial patients that have extended for a long duration.

DR. FISCHKOFF: In the adalimumab clinical program, the 1700 patients that I cited before represent every patient who has ever been in a Phase I, II or III study and has chosen to stay in a long term continuation.

DR. DR. SCHAIBLE: Similarly, every patient in a clinical trial is followed through five years, whether they stay on REMICADE or not. Then in

addition, we have substantial registries which -- I think you just look at our patients who are in them right now and who we have planned will probably take us close to 20,000 to 30,000 range of patients prospectively followed.

CHAIRMAN ABRAMSON: Dr. Gibofsky.

DR. GIBOFSKY: I defer to Dr. Elashoff with regard to what extent the number listed here is an appropriate power to get at the incidence and prevalence of lymphoma in other conditions.

The other caveat I would offer is, to the extent that the commitment is only for rheumatoid arthritis, as articulated here, I think we are not going to see the complete picture. If anything, we should strongly suggest that this data be collected for all indications for our patients with Crohn's disease, for ankylosing spondylitis, for JRA and so on, and not just for rheumatoid arthritis.

CHAIRMAN ABRAMSON: Dr. Williams?

DR. WILLIAMS: I have a little concern the way the patients have been selected. I have more comfort with the registry that was mentioned by Dr.

Schaible. But if we are only taking patients that were put in the initial studies, those are a selected group of patients that are not going to be equal to the standard patients that are treated with this drug.

DR. MAKUCH: I agree with everything. I think that for sample size I couldn't agree more with Dr. Elashoff. Probably she could do her calculation, I could do mine, and we all could. But I imagine it would be in the 5000 to 6000 range.

Secondly, responding to the remark just made about what kind of patients get into this, I agree that those in the clinical trials are probably very select. So it's been my experience that I have seen these kinds of studies being done where it is a hybrid. It is composed of both those from the clinical trial experience to get the longer term follow-up fairly immediately, as well as putting in perhaps the same number of new subjects into the clinical trials mix, so that you get perhaps a more general representative group.

The third thing about this question, I guess is a recommendation, and it came up with the

controls. The control selection really, I think, requires a lot more thought. I don't have an answer to it, but I think that, if five years down the road this were just done, I think we'll all still be looking at one another and still not know quite what to do. So I would really give a lot more thought to what the controls would be.

Fourthly, in addition to SEER, I think it would be -- even next year, to do an update, from what Dr. Tarone said, to update the analyses using the 2000 data from SEER that would become available.

Then finally, if one is doing these kinds of studies, to at least collect the kind of information that perhaps will allow you to better discriminate among different possible other explanations for lymphoma: Again, duration, dose, prognostic factors, concomitant meds, etcetera.

So I think that this is -- Question number 3 is a good start, but I think it really needs a lot more work. It's a very difficult question, in fact.

CHAIRMAN ABRAMSON: I guess, arguably, some of the patients who were followed were the very

difficult, more severe RAs which would be of particular interest to follow. Dr. Schaible and then Dr. Burge.

DR. SCHAIBLE: Right. I think two things about the registries. First of all, they do, I think, represent a more real life type of patient than you have in clinical trials, but there is also this caveat. That is that the patients who are going to be getting anti-TNF will be more severe than your comparator population. I can tell you, we have looked at the patients in our registries, and in both Crohn's disease as well as RA, you get the more severe patients getting treated with anti-TNF.

You may need to develop adjustment factors to adequate analyze those data.

DR. BURGE: The question specifically addressed the commitment of this 1000 to 2000 patients for five years, but as we have illustrated in our presentation, we obviously are observing far more than those patients from our initial clinical trials. RADIUS program has 10,000 patients, 5,000 of which are initiating etanercept and 5,000 patients who are on

other disease modifying agents.

The European registries have close to 2000 patients into them now. I think it's around 1600-1700, and continuing to roll all the patients that go onto TNF inhibitors in those countries.

So there is a substantially greater effort than just the long term extension trials mandated by the agency at the time of initial approval. In addition, we have -- again, trying to understand what the background epi is in RA has been challenging.

Dr. Silman did a great job of representing his view on the current literature, and we are trying to explore that further by doing an epidemiologic study in the Engenics Health Care Program to see if we can shed some more light on this.

So I think there are great efforts going on to try and help advance this.

CHAIRMAN ABRAMSON: Dr. Silman, do you want to make a comment?

DR. SILMAN: Just a brief comment on numbers and power. Unfortunately, it is not entirely analogous to a clinical trial, because even if you

have control groups who are not anti-TNF treated, they may have differences.

We attempted this exercise in the U.K., and we came up with a figure of slightly under 2,000. About 1900 subjects followed up for five years treated with anti-TNF would be sufficient to show a doubling in lymphoma risk at five years compared to background RA risk against an RA untreated comparison group.

CHAIRMAN ABRAMSON: For our oncologists, would five years solve the issue of latency and give us some comfort that that was an adequate amount of time to see an effect of the drug?

DR. KROOK: I don't really think it will. I'd like to make two comments, as long as I answered that question.

One, pathology -- I mean, the MedWatch which Dr. Cote showed us -- I mean, we've got 473 reports of somehow coding lymphoma, which really only 95 are biopsy proven. So what are we going to use? The best control that we have are the clinical trials, and having functioned in oncology clinical trials, my data managers are bugged all the time, both by

industry and cooperative groups, to are they alive, dead, what's happened, is there anything new event.

I think that, you know, it would be nice to use MedWatch or a group, but I don't know how we are ever going to sort it out in that group when we are not -- you know, to look at all these path slides and then, as Dr. Jaffe said earlier, we were talking that even the nomenclature in lymphoma is changing and may change again.

So I think the best group we have are those clinical trials. Now I'm not sure we are going to get more than that.

CHAIRMAN ABRAMSON: Dr. jaffe and Blayney, is five years enough to give comfort?

DR. JAFFE: I don't think so. Even if you look at the situation of post-transplant lymphoma, post-transplant lymphoma is not one disease. It is multiple diseases. Early on, you see the EBV positive polymorphic B cell lymphomas that can regress spontaneously. Late, you get more monomorphic lymphomas, and you get even T cell lymphomas and gamma delta T cell lymphomas, and probably each of those

subsets has different pathogenetic factors.

So I think you need very long term data, and I think you have to really look at the cases, because lymphoma is not one disease. I mean, we are talking as though lymphoma is one disease. It is multiple diseases, and you don't know -- You have to sort out what is due to disease, again what is due to treatment, and what is due to background noise.

DR. BLAYNEY: I would certainly defer to Dr. Jaffe on that point. I don't think we know. There are, as she says, many different diseases, but it is worth pointing out that lymphoma is, as an oncologist, one of the diseases which we do quite well at. Even if we don't get rid of the immunosuppression, we do put into remission a fair number of these patients.

So again, it is quite different from the secondary leukemias that are seen and secondary lung cancers that are seen after radiation. So bearing in mind that the risk of death from lymphoma is not 100 percent.

CHAIRMAN ABRAMSON: Dr. Elashoff.

DR. ELASHOFF: I just wanted to make a comment about the value of the registries. We saw some figures for one registry about eight percent attrition per year. Registries are only really valuable if the patients that you get into them stay in them for long enough so that you really have long term data on each patient.

If you get a lot of patients in and then they are lost to follow-up after six months, then you never get much more than six months information on people, no matter how many patients are in. So the whole issue of keeping the attrition rate low is extremely important to the potential value of any registries.

CHAIRMAN ABRAMSON: Dr. Manzi.

DR. MANZI: I think I would just like to make -- I agree with you about attrition, but I also think it takes a tremendous amount of support, financial support, to keep these registries intact for long periods of time.

I credit Dr. Wolfe and other people who have tried to do this, but it takes a commitment on

whoever is going to support it to have the staff available to get all the lost to follow-ups and accuracy in biopsy reports and everything that we are talking about that is critically important. I think, to their credit, they are doing probably a lot of this without the full support that it takes to do it.

DR. COTE: I'd like to concur with my colleagues who are also reticent to cut things off *a priori* at five years. I think there's some wisdom in that, because other information from transplants, to AIDS, to atom bombs have all shown that there are very late term effects.

I think therein will lie the real answer, is in long term cohort studies, but I'd like to bring the committee back for just a moment to this, the MedWatch program, the 158 cases of lymphoma that we know that do exist and for which we have very poor information.

What kinds of information shall we -- Is the juice worth the squeeze to go back and get the kinds of histology information, perhaps secure blocks and slides, perhaps do testing for EBV, perhaps find

out those kinds of questions that were brought up earlier in the day in terms of latency, between times of treatment that were begun and times of development of lymphoma? Is it worth mounting an effort to do that or requesting sponsors to do that at this time?

CHAIRMAN ABRAMSON: Before we address that, Dr. Williams had a comment. Then we will come back to that.

DR. WILLIAMS: We hear talk about comparator groups and control groups, and there won't be any. We are much more aggressive in our treatment of rheumatoid arthritis, and these are the best agents we have. So anyone who doesn't respond fairly dramatically to other agents are going to end up on these agents. So there really aren't going to be a good control group.

DR. KROOK: It's going to be historical, if any.

DR. WILLIAMS: We've heard the historical, and it hasn't been adequate for us today.

CHAIRMAN ABRAMSON: Right. I think just my own response to the question is the MedWatch is a

good way to maybe pick up a signal, but probably not a good place to go looking, digging for more data, since we have, in my own view, more sophisticated ways to do that.

I wonder, you know, between the Tennessee Medicaid database, this ARAMIS -- there's so many large clinical population medical care databases now, and I ask Dr. Siegel or a representative from the FDA, how is the FDA using these large population medical care databases to capture this information?

DR. BRAUN: We had a Request for Proposal that went out somewhere around a year ago at the FDA, and we are contracting with the UnitedHealthcare which is a nationwide medical care reimbursement insurance organization, and using its claims database, we are going to try to look at some of these questions, these adverse events that have been discussed today.

Roughly -- This is very rough -- there is around 4 million covered lives, but it is very instructive when you get into these databases and look at the number of patients who are taking the biologic agents for rheumatoid arthritis. They become very

small. It's amazing how you can start with 4 million covered lives, and you find 1000 or 2000 patients who are taking -- who are on etanercept or on infliximab.

You know, the adalimumab has not hit the really -- hit those kind of databases yet. So that is really a blank. It's very challenging, and as was mentioned, it is also expensive, certainly for us, because we don't have a large research budget. But we are trying to obtain independent data, as was mentioned, real world use of the products.

We have already -- I think we are confident that we will be able to demonstrate some results, but we won't be able to easily, if at all, answer these kind of questions, say, about can we demonstrate an increased risk of lymphoma or not definitively in patients on biologic agents versus some comparator, say, a methotrexate treated group.

This is an ongoing project that we have, and it is something that we can try to obtain independent information from.

CHAIRMAN ABRAMSON: Dr. Blayney.

DR. BLAYNEY: I think the insights are

going to be on a biologic level. As was pointed out, both by our pediatric colleague and Dr. Williams, people are going to get this medicine earlier in the course of the illness and, hopefully, improve morbidity, but that also gives them a longer chance to develop some of these untoward side effects.

I think that the juice is going to be on a biologic level and find out either who is at risk for these and how to treat them. We are not going to have a control group. I think the work of epidemiology is done. It now needs to move to the laboratory and our bench colleagues.

CHAIRMAN ABRAMSON: Dr. Williams, then Dr. Burge.

DR. WILLIAMS: Involving the question of juice and squeeze, I think that if what we are seeing is that the lag time is 600 to 800 days, we probably won't learn anything, and we'll come back with SIRs of 5, and we won't know anymore than we know now. However, if we are seeing the beginning of a group of patients that will develop lymphoma as a result of these therapies, then we may see higher results, and I

think it is still worth looking at it so that we are not missing something bigger.

DR. BURGE: I just wanted to respond to Dr. Cote in that what's the value? You know, is there value in going after this? Our personal bias is that, certainly, more information is better, and there's multiple avenues by which you can get data, clinical trials certainly, registries certainly, doing some work with epidemiologic work.

We actually feel it is also hugely valuable to try and pursue and get as much information as we can on these cases in post-marketing. We developed a standardized worksheet to go after specific issues on things like lymphoma, and we have been very successful at it.

We have obtained 70 percent of the histopathology reports. Again, that's not 100 percent, but certainly having more data is much more helpful in interpreting the situation than having less, and then when you can put all these pieces of the puzzle together, the clinical trials and the registries and your data from your post-marketing, we get a much more

complete picture.

So we think that it is not only useful, but it i s feasible to pursue, and again we are not going to get 100 percent of it, but it is very helpful.

CHAIRMAN ABRAMSON: Thank you. So the question, just to go back to the question: The companies are already following 1000 to 2000 patients and have registries of various kinds. Should the companies be asked to obtain additional specific types of information than what is already being collected?

I wonder if there is a comment from the committee?

DR. WILLIAMS: Again, we have already mentioned this, but all these patients come from trials, and I think the registry done by Centocor is going to probably give us more information. We need to get some patients who are not selected for the early trials.

CHAIRMAN ABRAMSON: Dr. Weiss.

DR. WEISS: Though it sounds like from the comments that came out as part of these discussions,

there's certain things that maybe it will be difficult to do in the post-marketing passive system, but to try to be a little bit more proactive in terms of things like the EBV association, things that there might be a window of opportunity to try to collect, or it's better to collect it up front than to try to go back maybe and hunt up this information.

So I'm just wondering about with this ongoing -- you know, either the registries or these long term extension studies, to go back and look and make sure that there is active case report forms that actually specifically have places to try to fill in the blanks with respect to things. And there generally are, but for things like concomitant medications or duration of treatment, but other things that are more difficult maybe like other concomitant medications, prior medical -- prior types of treatments, the EBV in particular, which may or may not always be collected.

I just want to know if the committee thinks it would be good to just sort of relook at what is being collected now in either these registries or

these extension studies that are going on, to just try to make sure that we get the biggest bang for the buck with those data.

CHAIRMAN ABRAMSON: I take it at this point, there's not been any standardization of the various registries by the FDA at this point. Is that correct?

DR. WEISS: The FDA isn't really -- you know, isn't running them, and we ask the companies to collect information and then, as you see, they have all gone on beyond just these open label extensions and developed registries of different kinds.

I mean, we haven't looked specifically to make sure that every case report form or every type of questionnaire is exactly the same. We certainly have highlighted that we are particularly interested in infections and malignancies and lymphomas, and that's been sort of the standard kind of theme throughout all of these.

CHAIRMAN ABRAMSON: Dr. Ilowite.

DR. ILOWITE: Having worked with one or two of the registries, one of the problems with the

registries is that, if they start a different biologic treatment, they are automatically kicked out of the registry, at least in the one I've been involved in.

Of course, that's just the kind of information we don't want to lose, someone who has been exposed to a series of biologic agents. So it would be nice to have cooperation among -- and coordination among the various registries.

DR. GIBOFSKY: I think that's an important point, Dr. Abramson, that you began and that Dr. Ilowite followed up on. That is, while ideally it would be nice to have one registry as per Dr. Silman told us. The reality is there are half a dozen of them or so, and to what extent we can strongly urge that there be common data collection by whatever format is being used for that collection, but common data collection of a common dataset that can be mined across studies, I think that would go a long way toward answering many of the questions that we have.

CHAIRMAN ABRAMSON: This could be a good role for the ACR, some professional organization to develop a collaborative effort with these outcomes.

DR. GIBOFSKY: If Dr. O'Dell is still in the room, perhaps he would like to speak to his experience in trying to get that project going. Or not.

DR. WOLFE: Actually, Dr. O'Dell did try to get it going, and it was the NIH that expressed disinterest in projects that were not hypothesis driven, and that's what really killed it. So everybody should know that, I think.

If you want to really know how to do it, you need to ask Dr. Silman who is doing it -- who is enrolling all patients and doing it really correctly, because he has -- The nature of the support he had and the nature of the government support is such that that's the way to do a study.

Now speaking for registries, the national databank that I run is not a REMICADE registry. It's a databank of all patients with rheumatic diseases, and we take them all, whether they are on drugs or not, and we continue them, and we follow them, and we get all medications, and we try to follow them over time.

I think one of the things that I think isn't clear from here is that what really is needed to collect. My experience with this is that the target moves. When the drugs first came out, no one quite knew that there was a tuberculosis, and two years went by before suddenly everybody wanted to know about tuberculosis, and then congestive heart failure came up last year.

It would be very helpful, I think, if there were some sort of a conference for database managers to try to understand how best to collect it and what needs to be collected as a very minimum.

Having said all of that, it is extraordinarily difficult to get this information, because you have -- Up to now, you have had -- You need patient consents for every single thing. Beginning April 1, the world is going to change, and if you think that it's difficult now, it is going to be very, very difficult to get this sort of information.

I think it is because no one has really quite understood the need for it or defined the need

for it that has really made it hard; and if we all got together and perhaps defined what we want to collect, that would help a great deal.

CHAIRMAN ABRAMSON: Dr. Weiss, any further information on this question?

DR. WEISS: Dr. Anderson.

CHAIRMAN ABRAMSON: Dr. Anderson, one comment.

DR. ANDERSON; I'd just like to make a comment. I think that the work that Dr. Wolfe has been doing is just admirable in setting up his data bank, but in addition, I think that, in addition to all the clinical information, you really need in these databanks information of a more health services type.

I would hope you wouldn't have to have too much of it, but just to know -- You know, the reasons for starting and stopping drugs aren't all clinical, and some of them have to do with whether the patient can pay for the drug or not or whether there are reimbursement mechanisms available to them for paying for the drugs. So that these factors may have quite substantial effects on drug choices and, I think,

should be considered in the analyses.

MS. McBRAIR: As a consumer rep, I think this would be extremely valuable data, and people with rheumatoid arthritis would be very grateful to have information that would be collected on them as people that have a very serious disease. I think Dr. Anderson's comment about the additional information to be collected is also important.

Rheumatoid arthritis has had its first focus because of these new biologics. It really wasn't studied very much as far as -- or didn't have a lot of answers to help people. So I think this has been absolutely wonderful that there are some biologics medications that can help.

I think we need to learn more, and a national database would certainly provide us with some wonderful information that would be helpful to all of us.

CHAIRMAN ABRAMSON: Before we move to the next question, I think a historical note is important, because you always want more data, but I think both the FDA and the companies need to be commended;

because I remember in 1998 we were worried that there wouldn't be follow-up and databases, and the FDA mandated. I think the companies even went beyond what was mandated, and we have a lot of information and a lot of new insights into this disease, even separate from this particular toxicity, that came as a result of this interaction.

So I think that's just a historical note from someone who was here five years ago.

Let's get to question number 5: Please discuss how best to communicate information about lymphomas to health care providers and patients. For each of the respective product labels, please discuss how the agency should present the data on the observed incidence of lymphoma, the degree to which the data suggest an association, and the degree of uncertainty about the association. Should the standardized incidence ratio with respect to the general population be presented? Should the SIR with respect to the RA population be presented? Should labels be similar for each product?

Before we tackle that specifically, Dr.

Siegel, can you just briefly give us -- remind us what the specific labels are right now? Remember, the HUMIRA label was fairly explicitly discussed, but to address this question it would be nice to know.

DR. WEISS: Well, we handed out -- We don't have an overhead or a slide of this, probably because it is so difficult to do. We handed out copies of the label.

I want to make a comment, that I hope you appreciate the difficulty of getting the entire label on one page, front and back, on a very large piece of paper, but we managed to do that. It took some time and maneuvering. So I hope you appreciate that, so you don't have stacks of paper to look through.

We have wording -- Actually, Abbott provided the wording -- the label for HUMIRA in their packet. I want to point out that that's the one -- because it's the newest information and because we had, adding onto the HUMIRA experience, the experience with infliximab, and with etanercept, to some extent, in our background, we had more information in the HUMIRA label with respect to malignancy and lymphoma

than we have in the other labels currently. But that is one type of question that we want to put to the committee, and we certainly talked to both Centocor and to Amgen about ways to update the label.

Everybody has been receptive to it. It's just a matter of trying to find the right balance. I don't know if would help to read what we have, if you want me to do that, so that the audience can hear it. I know the committee -- It is very small print, but we provided information in the warning section for the HUMIRA label on malignancies.

It says: "Lymphomas have been observed in patients treated with TNF blocking agents, including HUMIRA. In clinical trials, patients treated with HUMIRA had a higher incidence of lymphoma than the expected rate in the general population." Then it refers to the adverse reactions.

"While patients with rheumatoid arthritis, particularly those with highly active disease, may be at higher risk, up to severalfold, for the development of lymphoma, the role of TNF blockers in the development of malignancy is not known."

Then we also have a section -- If you go to the adverse reactions section, we have a little bit longer description in the adverse reactions section, actually more on the data.

We say in the adverse reactions under a section called "Malignancies: Among 2,468 RA patients treated in clinical trials with HUMIRA for a median of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma. The SIR for malignancies was 1.0," -- and we give the confidence intervals -- "and for lymphomas was 5.4" -- and we give the confidence intervals. "An increase of up to sevenfold in the rate of lymphomas has been reported in the RA patient population, and may be further increased in patients with more severe disease activity. See Warnings."

Then we describe some of the other types of malignancies that were seen in the HUMIRA database. Severalfold -- that is up there. Thank you, Abbott.

CHAIRMAN ABRAMSON: So let me just reframe, if I may, this question, which is that, in two parts, how best to communicate this information,

and then in essence, should the label pretty much for the other drugs be comparable to this? I think, if somebody would like to open the discussion -- Dr. Day has particular expertise in this area. I'd like to begin with her.

DR. DAY: I'd like to comment that, if there is the decision to go with one of the ways to represent the data, the SIR or something else, then it would be useful to have it be the same across all. Although a highly trained and specialized physician may know how to use all of them, it makes it very difficult to compare across labels when there's different forms of representation.

This question is basically a three by three. We have the three products by the three ways to represent information, and we have to consider what the nature of the data are in each case and whether specific information should or should not be provided. Once that is done, if we could agree that there is an appropriate way to represent the information, that would move us along quite a bit, but I would speak very strongly for the same method or format of

presentation of the information across labelings for these comparable drugs, especially since the same physicians will be looking at all of them.

CHAIRMAN ABRAMSON: So let's stick with that part of the question. Does anyone else want to address whether these labels should be different from the HUMIRA? That's one aspect of this. Dr. Williams?

DR. WILLIAMS: I don't think they should be different. I think they should be the same, and I thought that the statement under the warnings was applicable to all three.

When you get under adverse events, it was specific to adalimumab, but under warnings could have been to all three.

CHAIRMAN ABRAMSON: Anyone disagree with Dr. Williams?

DR. DAY: May I ask a question? I notice that there are boxed warnings for two out of the three, and if this -- We always have to decide not only what is the information but where shall it go.

CHAIRMAN ABRAMSON: Right. So the boxed warning pertained to tuberculosis. Is that what you

mean?

DR. DAY: Right. But if we should decide that this should be in a boxed warning, there would be implications -- as opposed to the warning section.

DR. WILLIAMS: I would argue against the boxed warning on the data that we have right now. I think what is stated there is enough to state that there is a concern, but we don't know anymore about it than what's --

DR. DAY: And I would agree with that. I'm just trying to focus in.

DR. SIEGEL: I'd like to thank the panel. It was a very helpful discussion. I just wanted to maybe provide a little history and just raise one concern.

We mentioned that, when we craft language for labels, that we do it based on the data we have, and the datasets for the first two approved TNF blocking agents was more modest, and we couldn't make as many conclusions or as many calculations.

With the database that was available for adalimumab at the time of its approval, we had much

more information. We could calculate an SIR with reasonable confidence intervals, and face the question of what to do with it.

We thought that the kind of wording that was used in the previous labels probably clearly didn't contain all the information that we had for adalimumab, and we crafted the language for adalimumab based on this additional information.

Now having gone back with the other products to collect this information, we need to make a decision about how those labels should be done, and I think the committee has given us good advice on that.

I do want to bring up one issue here, which is that one of the confounding variables is the activity and the duration of disease, and there is some thought that these factors may substantially impact the background rate of lymphomas.

Some people have raised a concern about a hypothetical company developing a new product who selectively studies their product only in very early disease or people with mild disease, who might end up

with a lower SIR potentially based on recruiting patients with less active disease and then being at some kind of -- in a different situation when it came to incorporating that language in the label.

Is there additional information that we should include in the label -- for instance, the average disease activity or the median disease activity in terms of, for instance, acute phase reactants at the time of beginning the product, the duration of disease before bringing in the product, anything like that that would be helpful to provide a common metric?

CHAIRMAN ABRAMSON: As a physician who tries to read these labels from time to time, the less you put in, the better, if it doesn't really add that much value. I think -- Not to be facetious, I think since we don't know for sure what that information means yet, probably the simpler, the better for the physician being able to digest what is going on.

DR. WILLIAMS: Also, the milder the disease, the harder they are going to be able to show disease modification, too.

DR. BURGE: Hello. I was just going to say, again, we do have a substantial database. Again, I know everybody would like to have an enormous, 30 million patient years of exposure, but we have a substantial clinical database. It is continuing to grow. We've got five to six years of clinical experience, four and a half years of commercial experience, and we do believe it is very important to communicate the data that we have in our package label, and we proposed a label addition in the fall of last year.

I'm sure that a lot of this -- We've been discussing this with the agency, and a lot of it was awaiting this discussion we would have here. It is certainly our position that we believe that products should be individually assessed, and they should be assessed on their data and, when discussing the appropriateness of the label, should reflect the data.

We personally, with our SIR in the 2 to 3 range, don't believe that the data from the etanercept experience elevates it to a warning in the label, and would just like to make that statement. But we do

believe it is very important to communicate this, and we are in this active negotiation and discussion with the agency to move this forward.

DR. LEFKOWITH: I wonder if I could comment. I wanted to follow up on Dr. Siegel's questions and comments that we have heard from Doctors Makuch and Tarone.

I think it is fair to put into the label the data that are derived from the clinical trials. The issue, however, is whether or not all SIRs are created equal, if you will.

I believe that, given the range of SIRs that are possible within the RA population, from one to 26-fold, small changes in trial population may make an enormous difference. Whereas, it may be informative to portray the SIR within the label, merely indicating the lack of -- without appropriate context, it may be hard to compare the rates, and physicians may make wrong comparisons.

I believe there is precedence within labels to state specifically that, that rates derived within different products in different trials cannot

be directly compared. I think that is more informative to physicians than simply stating a rate and stating that it means something, and having them draw inappropriate conclusions.

DR. VOSE: My name is Julie Vose. I am a lymphoma specialist from the University of Nebraska Medical Center, and I would just like to comment on the SIR.

I am usually on the receiving end of things that go on after patients have received different products in patients that have RA, but I think in patients that have RA, we know that there is a background rate that's there, and the oncology literature would say between 2 to 2.5, and that's very consistent with what we've heard today.

I think it is very important for us when we are treating our patients to look at the products that we are trying to compare, and the SIR is a very good way to do that across products, but also to keep in mind that we need to know what the background rate in RA patients is n that context, and also to the extent that the patients have with respect to their

disease status, and certainly the more severe patients would have a worse set disease and SIR.

So we need to keep that in mind. And I would be in favor of putting that in the label, but the data that we have is not conclusive that that is necessarily a causational. So I think I would be against putting it in a warning box *per se*. Thank you.

DR. SCHAIBLE: I would just mention there is some precedence here in how immunogenicity is labeled, and that there is statement in labeling on immunogenicity rates that these rates cannot be compared from one product to another because of a number of confounding factors, which I think we also have here in terms of the nature of the population studied and the fact that one or two lymphomas could make a huge difference in the estimate of the SIR.

DR. GIBOFSKY: Mr. Chairman.

CHAIRMAN ABRAMSON: Yes.

DR. GIBOFSKY: I think, as important as it is to determine what we put where in the label, I would hope we don't lose sight of the fact the

question asked is how best to communicate, and if the label is going to be the only place that we put it, we are missing a wonderful opportunity to get information out to the physicians and to our public.

I think we should be thinking in terms of rapid communication such as the ACR hotline, sister publications with the AGA, and primary care specialties who take care of our patients, communications through our patient representative organizations like the Arthritis Foundation and the Crohn's and Colitis Foundation we heard from today.

I think the label is one important place, but we should not spend an inordinate amount of time trying to put 2 point font into 5 point boxes and miss the opportunity to give the bigger message.

CHAIRMAN ABRAMSON: Okay. So just to follow up on Dr. Gibofsky's point, we should go to follow up the discussion how best to communicate. But before we move to that, I'm wondering if the FDA has any comments about the specific issue of the label from more opinion from the committee at this point?

DR. WEISS; No. I think that we heard

some very good advice. We struggle a lot with coming to labels and to updates on labels all the time. Agree, it's not the only or perhaps not even the best way of communication. It is has what the FDA has jurisdiction and control over. A lot of the other methodologies that were described are very, very good, but not ones that we mandate or have any particular say-so in, other than, you know, the label and Dear Health Care Provider letters as our main ways of trying to communicate, as well as things like any publications that have been done in this area and presentations. But the issue of whether or not there's identical label for similar products or different, and we try to explain, for instance, with the tuberculosis and infections, there are some differences based on the data that we saw, but there are other times, perhaps this being one of them, where the data may be different but may not be, because of some of the uncertainties and immaturity.

You know, again it's not an easy question, struggling to be fair and balanced with presenting the data. That's basically a comment I wanted to make.

But I very much appreciate the discussions and advice we have received thus far.

CHAIRMAN ABRAMSON: Yes, Dr. Anderson?

DR. ANDERSON: Yes. I appreciate that there's not much room on this label to put anything extra. But it would be -- and maybe these other avenues of communication would be the place for this. But I think it's not enough just to have SIRs. I think you need the absolute risk, you know, the excess risk, because an SIR can be misleading to people who don't appreciate just how low the baseline risk is.

So when other means of communication are used, then I think both ways of describing the risks should be included.

DR. TARONE: I'd just like to reiterate a comment I made in my presentation. I'm not really sure exactly what has been decided about what to put in the label, but I want to make the point again that, from a statistical point of view, there is no difference between the SIRs that have been reported.

Quite frankly, given the severity of the rheumatoid arthritis in the clinical trials for

adalimumab, I would have been stunned to see an SIR of 2.3. I would have been stunned. It's not consistent with what is known about patients with serious RA disease.

These SIRs are not significantly different. I don't know how you can put them in without having some indication of the variation. Again, I don't think confidence intervals are well understood. It's a serious issue.

I think the most serious issue is how you get across the fact that there is variation in these estimates that you expect to see, and they are not comparable just from a statistical point of view. There is no significant difference.

So it will be misleading, I think, to put in the individual SIRs and just have them there for people to see.

CHAIRMAN ABRAMSON: I would think that is also the sense of the committee, that if the SIRs are included, there has to be a very clear statement that there is no way that one can compare one agent with another based on these numbers, and that more

information is really required.

DR. WILLIAMS: In fact, my recommendation was they use the warning statement which was very generic and did not have SIRs in it, because it stated there was a risk and we didn't understand what the risk was.

DR. WEISS: Just to comment generally. In the hierarchy or the labeling rules, we generally put in information in a more descriptive term like you saw in the warning statement, and then usually specific data in the adverse reactions. That's generally sort of how the labels are set up. So that's sort of the reason why you saw the format that you did for the HUMIRA label.

CHAIRMAN ABRAMSON: Okay. So just to finish this segment and to pick up on what Dr. Gibofsky had started, what is the best way to communicate this information? Are there other suggestions in addition to what Allan raised? Yes?

MS. McBRAIR: This isn't exactly a suggestion, but I think it is important not to scare patients. People with rheumatoid arthritis have been

forever grateful for these medications, and I don't think anything that we've heard today is going to keep them from these. They have been wonderful.

So we just don't want to scare them either. They need to be vigilant. The physicians need to be vigilant. The patients need to be educated on how to be vigilant, and that seems to be the most important piece here for me.

DR. KROOK: Just a comment. As was said before, that most of the people who are getting these drugs are taking care of by sub-specialists. Somebody said 90 percent. So whenever, at last in my specialty, you sit down and say the side effects and the whatever, I think we depend on the physician, and if these are mostly all rheumatologists, then it's through their societies and through whatever that this would be done.

I think I heard 90 or 92 percent were prescribed by rheumatologists. So those are the people that should be to.

DR. BLAYNEY: I think the other comment to make about the label, and it may be obvious, but

that's what the people -- the sales force who calls on me uses. I would -- Any difference is going to be brought to my attention, regardless of how carefully I read the label.

CHAIRMAN ABRAMSON: So the best way to educate doctors is to make one better than the other. Dr. Siegel.

DR. SIEGEL: The other part of question 5 was whether the SIR, with respect to the general population, should be used. And then whether the SIR, with respect to the RA population, should be presented.

I wonder if we could get some specific comment on that. If it should, what would you use as the expected rate in the RA population? Would you use 2.2, and what about varying rates with different levels of disease?

I understand the difficulties, but it would be helpful to have some comment.

CHAIRMAN ABRAMSON: I think it's important. I think everyone would agree that it is important that the RA SIRs be in there, and that the

range for severe disease be noted, can be at this level and even higher, because that is the only context that this information can be dealt with, I think. I don't if people have different comments on that.

DR. DAY: I'm wondering if the people who are concerned about providing the SIR have more comfort in thinking about having them provided for both the general population and the RA population. Would that not ameliorate their concerns?

DR. ELASHOFF: I'm not quite sure I understand. Are you talking about saying the SIR as observed in these trials and the SIR for RA compared to the general population from prior epidemiology data, or are you talking about letting people divide the one by the other, which I would be strongly opposed to?

DR. SIEGEL: One possibility -- and it would be very difficult to calculate and very problematic -- would be to say "the appropriate comparator for calculating an SIR would be a comparable patient population, namely a rheumatoid

arthritis patient population."

To do that, you need to have an estimate of what you would expect the rate would be in that patient population, and you could calculate an SIR based on those assumptions. If it was twofold higher, say, than the general population and you calculated that the RA population was twofold higher, you would call that SIR 1 perhaps.

That would, of course, be very problematic, because it depends on what you choose as the SIR for rheumatoid arthritis compared to the general population. So that is really what we are asking, if you are comfortable with the way the HUMIRA label, for example, is currently expressed or if you think it should be done in relation to the RA population.

DR. WILLIAMS: I personally think using SIR is going to be more confusing than it is going to be helpful to the average physician or person that reads the label.

DR. DAY: What would you recommend instead?

DR. WILLIAMS: I don't know, but I had to educate myself on this for this panel, and I didn't know about SIRs before we got into this panel, and I'm just thinking that there are so many areas that we have discussed and so many variations that you are going to end up with quite a long statement if you have to explain the SIR in the normal population and the SIR in the rheumatoid population and the SIR in the patients who have had lymphoma.

CHAIRMAN ABRAMSON: Currently, in your label for HUMIRA you do say that the RA SIR is higher than the normal population. You cite a reference, and that may be sufficient. Dr. Boscia.

DR. BOSCIA: Dr. Abramson, I'm going to go out on a limb a little bit here. I'm going to get a little provocative. I'm outside my area of expertise, because I'm an infectious diseases trained physician, but this committee is very familiar with NSAIDs and Cox 2 inhibitors. I mean, you deal with them all the time. You've dealt with them in the past.

It's my understanding that for NSAIDs and then even when the Cox 2 inhibitors became available,

that the incidence of GI bleeds has basically been registered as a range for the different products, and it's done that way, I think, partly to prevent one competitor from differentiating themselves from another competitor based on noncomparative data.

I think it's been pretty much agreed that, in order for a competitor like a Cox 2 inhibitor to be able to differentiate itself from an NSAID in GI bleeds, they've got to do a very large comparative trial or some sort of trial to show that difference.

So because we don't have comparator data in comparative trials, and because the populations have been so different in the trials in some instances -- and that was one of the reasons why I put up our early RA study versus our DMARD resistant study, because there were no lymphomas in early RA and there were four lymphomas in DMARD resistant RA.

I'm just wondering if -- I said I was going to be provocative -- if it would make the most sense to list a range for the different competitors. I just thought I would mention it.

CHAIRMAN ABRAMSON: I think, in the case

of the NSAIDs, they all have the class statement that they may all cause GI toxicity, and I'm not sure that that's necessarily -- that that statement should make a better range is pertinent to this discussion.

Dr. Paulus.

DR. PAULUS: I'm Hal Paulus. I'd rather not see any SIRs in the label or risk ratios, particularly for these rare events. If I'm a patient, I don't want to know if I'm twice or ten times more likely to get something than somebody else, if I don't know what the likelihood is that somebody else is going to get something.

So what you would like to know is, if I start this drug, what's the chance that I'm going to get a lymphoma. You can say that for the general population the chance of developing a lymphoma at sometime in their life is one out of 1000 or one out of 10,000, and for patients with rheumatoid arthritis it's one out of 500, and with this drug it's in the range of the RA population or whatever range it is.

Then the patient can say, well, I'd take a chance of one out of 500, because I think this stuff

works. But if you tell them that the SIR is 5.6, they don't have the foggiest idea what it means, and the doctor doesn't know either.

DR. GORE: My name is Jeff Gore. I work at Wile Medical College of Cornell University in New York, and I was a member of the steering committee for RENAISSANCE, and I look at -- I evaluate drugs from time to time.

I'd like to make an observation here that may be worth thinking about. You all know this, but I'd like to state it anyway, and it's a follow-on to something Dr. Boscia said a few minutes ago.

He pointed out that the populations that are studied with the different agents are different and, therefore, it is hard to compare them and lump them together when you talk about writing a label.

I think another point has to be made, and Dr. Siegel made it earlier, but I want to state it in a different way. When you have substantially different molecules, two substantially different molecules, and they happen to share one pharmacological effect, if you think of it that way --

in this case, doing something to block the effect of TNF alpha -- when they share one pharmacological effect, it doesn't mean that they share any other pharmacological effect.

In fact, all drugs have multiple pharmacologic effects, and we don't even know all of them. The clinical effects are the net of the pharmacological effects. If we don't know the pharmacological effects, it's hard to trace a given pharmacological effect to a clinical effect.

Knowing that, the FDA always asks for data. They do a body count, and that's what's been done here. I think the suggestion would be that it would be useful to do what the committee seems to be doing, which is to say we don't have all that much information here. We have some suggestive or tantalizing suggestions, suggestive data, but nothing that really hits the mark to allow us to confirm or prove something with reasonable certainty and, therefore, we want more data.

Rather than lumping together the data from drugs that have been studied in different populations

and have multiple pharmacologic effects, of which they perhaps share one, and maybe they share more than one, maybe it's better to get more data.

So I just offer that as an observation.

CHAIRMAN ABRAMSON: In view of the time, let me go back to Dr. Siegel. In terms of this question of labeling, is there anything -- Obviously, there is some complicate issues to be addressed. Is there any final comment you would like to make on this?

DR. SIEGEL: No. We really appreciate the committee's advice. I think we've gotten the information we need from you.

DR. WEISS: I think we got a good range of suggestions, and I think we are going to take that back home and reconsider things, but we have a lot of good material to work with.

CHAIRMAN ABRAMSON: Okay, thank you. We are going to take a break in one minute, but I think, if we looked at question number 6: Please comment on the incidence and types of other malignancies observed in the TNF blocking agents. Do these data raise any

concerns at the present time?

The sense is not, and we can deal with that question that way.

Okay, why don't we take a ten-minute break and come back to do the last question at about 4:20.

(Whereupon, the foregoing matter went off the record at 4:13 p.m. and went back on the record at 4:31 p.m.)

CHAIRMAN ABRAMSON: We are going to go to the final two questions, and as people are taking their seats, I will read question number one.

Please comment on the data observed in the randomized controlled trials in patients with New York Heart Association class III and IV heart failure as well as the spontaneous reports of adverse cardiac events in patients with RA. Is it reasonable to discuss CHF related safety concerns in labels for all TNF blocking agents? Other than product label changes that will caution use in patients with preexisting CHF or who develop CHF while on treatment, should the companies be asked to develop additional procedures for congestive heart failure risk management?

I'll open that up to members of the committee. Yes, Dr. Makuch?

DR. MAKUCH: Yes. This was an interesting situation. I'm looking at the FDA comment that says there were deleterious effects of infliximab in the CHF patients and that in etanercept there were concerning trends in CHF patients.

So two comments. One is that there does appear to be a discrepancy in opinion or difference between the two drugs with respect to the effect on CHF.

Secondly, even within Enbrel itself, there is a discrepancy of results within the two trials. Again, I wanted to focus a little bit more on the futility aspects of those two trials, because I'm trying to understand both this between drug as well as within drug distinctions occurring.

So I was hoping that, one, there would be a further clarification of the futility rule and its relationship, if any, to safety in CHF in particular, and secondly, just to know more about the safety data at the time the trials were stopped.

CHAIRMAN ABRAMSON: I understand Dr. Packer is a consultant with Centocor today, and he was a principal investigator on these studies. Dr. Packer, would you mind coming to the microphone and addressing some of these questions, please?

DR. PACKER: My name is Milton Packer. I'm from Columbia University. I guess I sort of hold myself responsible for some of these issues, since I was the senior author on the first paper to ever report that TNF was elevated in heart failure. It might be a therapeutic target.

So a lot of the enthusiasm that pharmaceutical companies had for blocking TNF which has not paid off in the area of heart failure, I guess our initial paper sort of led them astray.

I also, I guess, have the dubious hat of having been the co-principal investigator for the heart failure trials for both sponsors and, although I am here today as a consultant for Centocor, I guess I can discuss any information which is publicly available on either trial or from the heart failure perspective.

CHAIRMAN ABRAMSON: Dr. Makuch, do you want to address one of your questions to Dr. Packer in terms of the methodology?

DR. MAKUCH: Well, I guess it was just to explain more about the futility index. I mean, in particular, as mentioned earlier, there is sort of a one-sided hypothesis to this, just looking at the efficacy component, and there was not the other side of the coin where one would also be simultaneously looking at a safety issue.

Of course, if you stop the study because you are only seeing a lack of efficacy, but you are sort of going down the safety concern side, but you stop only because you have the efficacy issue at heart, well then, almost by definition you are not going to see a safety issue, not because there may not have been one, but perhaps because the efficacy component drove the futility index decision to terminate the trial early, and then you would not have the opportunity, if you will, to have seen the safety issue.

So that's where, I guess, I need to

understand more fully what the futility index definition was, how it was applied in this situation, and again what the safety data then were at the time that the trials were terminated.

DR. PACKER: I think probably the best way I can answer that question is to again refer to the public presentation of the data and the futility and the public presentation of the futility rule.

When the results of the trial were first presented, they were first presented at a European Society of Cardiology meetings in Oslo about -- I guess about a year and a half ago. At that time, the presentation indicated that the way the futility rule worked -- and I just wrote this down -- was that the trial would be stopped because of futility.

If the effect of the drug was sufficiently unfavorable to rule out an even ten percent benefit, that would correspond. That is the precise wording of what was presented during the presentation. Does that help you? Does that answer your question?

DR. MAKUCH: Okay. So is the answer then to my question that, if it were -- if the trial was,

in fact, going on the side of increased safety concern on the part of the active drug, then it would have been terminated prior to it actually crossing that threshold?

DR. PACKER: Yes.

DR. MAKUCH: Thank you.

CHAIRMAN ABRAMSON: I'll ask Dr. Siegel, because we've discussed the CHF earlier in the day, what the status of the labels is right now for each of these drugs.

DR. UNGER: Well, when the results of these trials became available, there were -- Basically, for the Enbrel label there was a precaution in a CB -- changes being effected, and that precaution is in the label that you have in front of you.

For REMICADE, there was a contraindication and a warning placed in the label. Again, that is in front of you. For HUMIRA, there is nothing in the label.

One of the questions that we have -- it is kind of implied in the question here -- is sort of similar to the question earlier when we were talking

about lymphomas for the committee. Would all TNF blockers deserve the same language for heart failure? Does it appear to be a class effect or should -- maybe there would be a simple statement in terms of, you know, class effect, and then specific information where specific information exists.

Obviously, we have a lot of specific information for etanercept and a fair amount of information infliximab.

CHAIRMAN ABRAMSON: Is it the precedent might be the TB warning or the TB difference -- different language for infliximab and etanercept with regard to TB precautions, one having a black box and the other just a comment about -- a caution?

DR. SIEGEL: I guess what Dr. Unger was saying would be similar to the situation with TB in that all the labels contain something about TB being observed in patients receiving TNF blocking agents, including the agent that is in that particular label, and they would have more specific language, for instance, the box warning, if the data indicated that.

CHAIRMAN ABRAMSON: Dr. Williams.

DR. WILLIAMS: To address the question, first of all, I think that, since two of them have looked at it and found that it may make heart failure worse, and the third one didn't look at it, it ought to probably be in there as a caution on all of them.

I would probably make it similar to all three and make it a caution rather than the strong contraindication given to infliximab and state that it should be used with care in patients who have congestive heart failure.

DR. BOSCIA: We at least need a contraindication at doses above 5 milligrams. I mean, clearly, we had a problem with mortality at 10 milligrams, and we at least need that for patient safety.

CHAIRMAN ABRAMSON: Dr. Elashoff.

DR. ELASHOFF: Okay. I don't have any particular comments on what should be said in the label, but I do think that the data suggest that, for the two compounds that it was studied, the data are suggestive in both cases that one needs to be concerned and that the only reason we aren't concerned

about the other one is that they came along late enough not to make the same mistake and study it.

So I think we should have relatively consistent labeling on all three based on the data we have at hand.

CHAIRMAN ABRAMSON: So as a practical question, one would be suggesting that the Enbrel label to be changed to be more compatible with the REMICADE label?

DR. WILLIAMS: I have to agree that if you've got mortality, that we have to have the contraindication on infliximab, but I think that the Enbrel label more accurately reflects things, and I would make the adalimumab label more like the Enbrel than I would more like the infliximab.

I have a question for Jeff. I don't know what he is asking when he says asked to develop additional procedures for CHF risk management.

DR. WEISS: In all fairness, I wrote the question. So I can't blame it on Jeff, but I'd like to. I guess -- I think it stems from some of the analyses and data that Dr. Unger presented.

We already know that people with preexisting heart disease, you know, should not be taking this product. We know, though, that heart disease is clearly a big health problem in the United States. It's clearly a big problem in people with RA. In fact, I heart from my rheumatology colleagues that cardiovascular disease is probably a higher -- it's elevated perhaps in the RA population. I think everybody is nodding their head. So I'm glad I'm not speaking in error here.

So with that as a background -- So we have the area in the specific disease setting in CHF where we know it's a bad thing and we shouldn't do that. Then we have here the indicated population, large population, that are taking TNF blockers. Some of them are clearly going to have underlying heart failure. Some of them are going to have a history, predisposing factors, maybe not outright failure at the time that they are started on therapy, but a history of it.

One of Dr. Unger's analysis, albeit somewhat -- definitely an exploratory *post hoc*

analysis, tended to imply that even people with lesser degree -- at least in one of the trials -- I guess it was the RENAISSANCE trial, the North American trial, those with New York Heart Association II where you wouldn't necessarily expect maybe these problems had perhaps more -- again, caveats about being the subset analyses and retrospective -- that there was concerning events in people with less severe forms of heart disease.

So how does that help you in terms of trying to advise patients, what kinds of information to put into label? Should there be other methods that the companies could do, just like they did with TB. There it's a little bit clearer. You can do screening and prophylaxis.

Are there things that could be done with people with predisposition to heart failure, with existing heart failure of some degree, who have bad RA and may very well benefit from these products in terms of trying to improve the safety profile?

Ellis, if there is anything else you want to add --

DR. UNGER: Another caveat is that, if I'm not mistaken, heart failure is one of the most -- maybe the most common diagnosis for a discharge summary, and there are many patients who are actually misdiagnosed with, "heart failure."

So again, that suggests that it might be worthwhile to have some kind of a screening test to see if a patient actually has heart failure. Again, we are just kind of throwing out these ideas.

DR. WILLIAMS: I don't know that I can address that specific what screening tests should be done, but there may be people with mild heart failure who would benefit from these medications where we can treat the heart failure and still allow them to take these medications. That's why I didn't want to see it as a strict contraindication.

I can understand at higher doses, but as long as we can manage the heart failure, they may still benefit from the medications. But we have to be aware that we may make the heart failure worse by giving them the medication.

CHAIRMAN ABRAMSON: A question that harks

back to the capturing of information going forward and standardized data being collected. So the question is: Is heart status part of the information that is being collected in these prospective databases where lymphoma has been the primary outcome of interest?

DR. WOLFE: Do you want me to answer that question or do you want to go first?

CHAIRMAN ABRAMSON: I guess one of the companies could address that.

DR. WOLFE: Okay. In the registry that we have, we collect all information about cardiovascular diseases as well as all drugs that people are taking for cardiovascular diseases, and we also ask them specifically if they have had myocardial infarction, congestive heart failure, and we get all medical hospitalization records.

So we have a paper that has been submitted for publication. Based on 7,000 or so patients who were not taking any TNF agent, the rate of heart failure -- prevalent rate of heart failure was about 3.9 percent, that it was 2.8 percent on people who were taking these drugs.

The new cases which developed in people who had no previous history of any cardiovascular disease suggested was about .18 percent in one group and .20. These are all adjusted for severity differences.

So we found -- and we then did sensitivity analyses to look to see whether the warning from the FDA might have reduced the participation of people with heart failure by looking prior to the warning and also to making other adjustments. As far as we can see, we do not see any effect -- any increased rate of heart failure, and there is actually a suggestion in the other direction.

Now the other point is that these were -- Many people don't know they have heart failure, of course, because when you get in the hospital and they do tests, then they diagnose this. But the studies that you are talking about are New York Heart Association III and IV, which are very, very different than what is seen in the clinic generally.

So I think the warning may be overstated.

DR. UNGER: Actually, the RENAISSANCE and

RECOVER studies included patients who were -- about a quarter of the patients were functional class II.

DR. BLAYNEY: However, they did -- The patients in those studies did have an ejection fraction of less than 30 percent. So these are not, you know, mild heart failure people. These are people with damaged hearts.

DR. UNGER: Compensated heart failure, I would say.

DR. BLAYNEY: Yes, but they do have some underlying --

DR. UNGER: Dr. Packer disagrees, and he was there.

DR. PACKER: There is no relationship between ejection fraction and severity of heart failure. Ejection fraction -- The only way we judge severity of heart failure is really by symptoms, and the relationship between ejection fraction and symptoms is pretty poor.

Almost every trial we do enrolls people with ejection fractions less than 35 or 40 percent. Some of those trials are mild heart failure. Some are

moderate. Some are severe. So you can't make the judgment of mild based on the ejection fraction, plus the fact, frankly speaking, although it is not good medical practice, most people with heart failure in the United States are managed without an ejection fraction -- without an ejection fraction measurement. Yes, they have an ejection fraction. We just don't measure it.

CHAIRMAN ABRAMSON: Yes, sir?

DR. GORE: Again my name is Jeff Gore. I'm also in New York like Milton, but at a sister institution, the Wile Medical College. I'm going to -- but we share a hospital. It's the New York-Presbyterian Hospital.

I'm going to try to respond to the questions you have raised and the question as it's written. But before I do, let me for Bob make a -- read the formal -- Milton stated it, but the formal written -- Whoops, what happened to that slide, please? Ah, there it is.

There is the formal written statement of the early termination rule. The DSMB recognized that

even by conservative bounds that adjusted for the interim nature of the analysis, the confidence interval for this estimate ruled out a ten percent benefit from etanercept, crossing the established boundary for lack of efficacy on the morbidity mortality endpoint.

It was on that basis, that finding, that the trial was stopped and when RENAISSANCE was stopped, RECOVER was stopped, because it was perceived that it would be inappropriate to continue it if we were stopping for futility.

Now having said that, let me move on. Milton just made one of the key points here. Screening for heart failure means you take a history and you do a physical exam, which is being done, and you ask questions and all that kind of stuff, and he can tell you, obviously, chapter and verse about that.

Let me talk just a little bit about the data in response to the question here. In terms of worsening heart failure or death, looking at the data we have just from the etanercept studies, because those are the only data that I really know well, there

was a modest tendency in RENAISSANCE for worsening. There was a modest tendency in the other direction for improvement in RECOVER, very modest. I think nothing of either of them, albeit as Bob pointed out earlier, the follow-up time in RECOVER was less than in RENAISSANCE because of the early termination.

If you put the two together in RENEWAL, there was a modest tendency toward worsening. If you believe in statistical adjustments -- and those are, of course, arbitrary algorithms. But if you believe in adjustment at all, at least qualitatively, the existing modest tendency toward worsening becomes less of a modest tendency toward worsening.

In any event, in any of those analyses you do, even with observational statistics, not adjusting for all the things that you would have to do if you were talking about an efficacy endpoint, the consistency of those data don't reach the level where you could draw a firm conclusion. Nothing is close to statistical significance --

CHAIRMAN ABRAMSON: Excuse me, Dr. Gore, if I may just -- What I'd like to do is go back to the

question, which is the label change, for now.

DR. GORE: Okay.

CHAIRMAN ABRAMSON: I don't think we need to hear more about the study, just because of -- in terms of addressing the question here.

DR. GORE: Oh, all right. I'm sorry. I was responding to the question that was written here.

CHAIRMAN ABRAMSON: Right. So do you want to just hold your comment just for a second, because I don't want to get too diverted from the chart. You are addressing the screening, what screening implementation should be, additional procedures for CHF, because that's the second half of this question other than label?

DR. GORE: Well, I was actually sort of addressing the issue of whether there is something here to label about, but okay.

CHAIRMAN ABRAMSON: Why don't we just -- If you just hold that thought, because I do want to come back to the question of label.

Right now we have two labels existent. For etanercept we have a precaution, and for REMICADE

we have more of a warning. That's pretty much established. Are we being asked to address whether that should be changed?

DR. WEISS: Well, these -- Certainly for the etanercept, it was submitted as what's called a CBE or changes being effected. That means that the companies can submit the changes, implement the changes. The FDA has the opportunity to review them, but the idea is that safety information is important and, while FDA is reviewing it for more data, meanwhile the information isn't being communicated at all.

So, therefore, in one of the last PADUFA negotiations there was a change. So that that information could actually be directly added to the label without sort of an FDA concurrence, while then allowing review to happen.

So there's opportunities to -- I mean, things are never fixed, because there is always new information coming up, whether it's safety or new efficacy in the cases. So these labels are very nonstatic, and we are constantly changing things.

Right now, the way they are is what you see before you, but things have not been finalized. There's still some discussions going on and still some additional data under review. So it is a good opportunity, if not now, at some relatively future day soon in the future to make any changes, if the committee feels that there are important changes that should be made, whether or not the wording is in the appropriate sections in the label or whether or not there should be more similarities, etcetera. So --

CHAIRMAN ABRAMSON: Okay. So, Dr. Gore, if you wouldn't mind, could you focus on that issue, whether you think the proposed label should -- What comment do you have on the label for Enbrel?

DR. GORE: Yes. I think that the label, as it exists now with the statement about, you know, there being some data that suggests maybe something is going on, is perfectly adequate; because that's all you can say from the information that is available. The data just don't go any further than that.

If you want me to support that statement with some information that you haven't heard about

today, I'd be happy to do that, but --

CHAIRMAN ABRAMSON: I think we are okay, actually, on the Enbrel, unless you are suggesting there be a change. Yes, Dr. Packer?

DR. PACKER: I just want to express a personal view based on my own view of the data. I think it also reflects the view of many people in the heart failure community, and it's a view that will be unpopular with everybody, and maybe I'll be able to get home after stating it.

That is that I wouldn't give any of these drugs to anyone with heart failure, and people with heart failure are fragile. When they get worse, sometimes you can't make them better. We are talking about some major issues here, issues I have personal concerns about.

I don't want to get into details as to whether the labeling should be the same or different or whatever, but I think that there is a concern such that people with heart failure in general shouldn't receive these drugs.

CHAIRMAN ABRAMSON: So that gets at the

specific question, should all the labels, and I guess particularly -- What are the plans for the HUMIRA label?

DR. WEISS: Recognizing that that is clearly not at all mentioned in the label and that there does appear to be this -- you know, two out of the products have shown something, that there should be some changes. I think that the company would agree. So we will be discussing and have already tentatively approached the company about making some changes to the label. This discussion would help, I think, facilitate that.

CHAIRMAN ABRAMSON: Yes, Dr. Gore?

DR. GORE: Yes. I'd just like to point out -- I mean, obviously, Milton's opinion comes from years and years of working in this area and is a very important opinion. But I think it's not right to go beyond the data that we have, and I think it's very important to remember, as I said earlier, we are talking about -- When we look at the three agents that we are talking about here, we are talking about substantially different molecules, and it's not really

reasonable, I think, to lump the results together and say the worst one is what tells us how they all work.

I think you have to say what you've got and give whatever cautionary information you have, and then collect more data rather than saying, well, you know, what we have now meets the test, and by golly, nobody should get this stuff.

So you know, in terms of drug use as well as drug approvability, the issue of efficacy and the issue of safety alone aren't the criteria for use or approval. It's the relation between the two, the benefit to risk relation.

What we've seen from these data, at least from the etanercept data -- I don't know about the others, but from the etanercept data we've seen a very modest suggestion that something may get worse. I could go on and defend that, but I won't.

We've also seen a tremendous benefit. I think, if you present that information to physicians, they can make a decision about whether the relation of expected benefit to known or even suspected worse case risk in patients with heart failure justifies the

administration of the drug. I think that's very important to remember.

CHAIRMAN ABRAMSON: So this is the difficult question of class effect versus what data we have. Dr. Elashoff?

DR. ELASHOFF: I just wanted to comment on the issue of the statement that the data show only a modest risk, and it has to do with the point that Dr. Makuch was making. That is that the RENAISSANCE trial was stopped as soon as there was any real evidence at all of risk and that it was prevented from ever going on and possibly showing that the risk was higher.

The stopping rule prevented us from ever demonstrating a bigger risk. Whether there might have been one or not, the statistical stopping rule that was used prevented us from ever seeing a bigger risk.

CHAIRMAN ABRAMSON: Okay. Perhaps if there is a sense of the committee, you have some discussions ongoing on infliximab and etanercept that are graded. They are not the same, and you have discussions with the Abbott company about some potential statement, as we understand it.

I think, unless someone else on the committee has a feeling that that shouldn't be the way to go forward, we're probably not going to get much more out of this part of the discussion.

DR. WEISS: I just have something that is a little bit unrelated, just for a second, just the comment that our statisticians made, which I think is very important to highlight, and it's not just with heart failure in these trials or with RENAISSANCE and RECOVER but in other settings as well where trials are stopped early for futility and may or may not have demonstrated harm and the whole concept that, you know, you don't -- I think our view is that you don't have to prove harm to the same level that you prove efficacy.

So I mean, you know, just -- It's sometimes a misnomer. I mean, it's true that the trials are stopped for futility if some of them happen to show some adverse trend. It's important to just look at those data and not just brush it under as, well, it's just stopped for futility, and that was it.

I mean, clearly, there are trials that are

stopped for outright harm, but in some of these kinds of more gray areas where they are stopped early and you are not going to know the answer, and you are never going to be able to do those studies anymore to actually, you know, prove anything beyond -- you know, to the level that you would want to prove efficacy.

CHAIRMAN ABRAMSON: With respect to the last part of that question number 1: Should the companies be asked to develop additional procedures for CHF risk management?

I could start off with a comment that we don't -- I think a label is an appropriate thing to do. Asking companies to do additional risk management may be premature or not -- in my own view I'll express for the committee, and we can have comments -- but do we need, like the other discussion, more information and as we collect more data on treatment with these drugs, we need to get a better sense of the risk of CHF in patients being treated with TNF blockers. But my own view would be not to ask for new initiative on their parts, given the information that we have.

DR. DAY: There are a variety of risk

management tools available. Did you have any in particular in mind that you thought might be useful here? I mean, it goes all the way from stickers on drugs to patient registries, physician registries and so on. There's a whole gamut here, and we are in a caution mode. But are there a couple you would like us to think about?

DR. WEISS: I'm really sorry I put that into the question. I guess I was thinking more along the lines of whether or not there's specific patient screening type of things that could be done. You know, we've already talked about patients should be closely monitored, you know, carefully evaluated for worsening, and should be, you know, stopped in some cases. But whether or not there's any other ways to try to evaluate patients that could be ask for. But that was mostly what I was thinking.

CHAIRMAN ABRAMSON: Okay. The last question is: Please comment on any other concerns based on the safety updates provided and any specific actions the agency and the various companies should undertake to address them.

I think we may have covered the waterfront here.

DR. WEISS: That was just in case -- I mean, we did focus a lot on lymphoma. We focused on CHF as a second area. We did have a little bit of information and update on TB and addressed that. Some of the companies presented a little bit more of the update.

A lot of this was covered in August of '01 We just threw that out there as a sort of open-ended question in case there's something else that the committee wanted to call to our attention, to have us consider. We'd be happy to entertain that, but if there isn't anything, that's also fine.

CHAIRMAN ABRAMSON: I'm not sure if there isn't anything or it's just five o'clock. Any comments, additional comments? No. Okay. So I guess we can adjourn. Thank you all very much.

DR. WEISS: Thank you, everybody on the committee and guests.

(Whereupon, the foregoing matter went off the record at 5:03 p.m.)