I would like to specifically recognize important and significant developments that have contributed to this achievement. First, the advances have only been possible through a steadfast investment in basic and clinical biomedical research. These have provided insights into the pathogenesis of rheumatoid arthritis, and the conduct of rigorous clinical trials that have documented the effects of treatment on the disease course.

The Arthritis Foundation has been particularly pleased to play a small part in supporting this research.

Second, the biotechnology and pharmaceutical industry has successfully built on this science base and has developed effective products that modify biologic pathways important in this disease.

The development of targeted drugs specifically for use in rheumatoid arthritis is a new and important direction for industry, and, finally, we would like to recognize the agency for review and revision of labeling indications of drugs used in the treatment of this disease.

Clear statements as to whether a drug improves symptoms or prevents joint damage and destruction is a major step forward in allowing prescribing physicians to make more intelligent decisions and informing patients as to realistic expectations from drug treatment.

We consider studies that look at a more primary

role of aggressive treatment early in the course of rheumatoid arthritis as a logical next step, as a way of better control of this disease, and hopefully to minimize the long-term consequences of this chronic disease.

Early diagnosis and early treatment are key strategies of the Foundation's National Arthritis Action Plan as we work towards Healthy People 2010.

We indeed look forward to the next decade with hopes that scientific research will uncover additional mysteries of this disease and will not only allow for better control but ultimately methods to cure and prevent it.

Thank you very much.

DR. ABRAMSON: Thank you, Dr. Klippel.

Finally, we have a letter to be read to the record by Ms. Reedy.

MS. REEDY: From Kara Gregory in Darien, Connecticut.

"I send you the perspective of a mother of a young child, seven years now, who was diagnosed at age four with systemic onset JRA. Enbrel has been the only drug that has worked for us, and I wish the drug had been available to us three years ago.

"My son was on numerous drugs with many adverse reactions, and his swelling and pain persisted to the point

where he was unable to walk, eat, move his head during his sleepless nights due to pain, even had to be physically turned over. He was unable to do anything himself.

"We tried methotrexate, too, which is what rheumatologists usually prescribe first now, and it had adverse reaction in the liver and horrible mood swings with prednisone and some of the NSAIDs.

"Rheumatologists told us our son would probably never get better, and he would probably never respond to any drug. That is when we went the natural route which helped a little, and then Enbrel was approved, and we noticed the difference immediately, and within four months, he was running, climbing, and his swelling is now almost undetectable.

"I believe Enbrel to be so much safer than the current preferred treatment by rheumatologists, and when a child develops RA and does not respond to other products, then I truly believe they should be given Enbrel before any of the other DMARDs and other drugs out there.

"My son has been on Enbrel for 18 months, and the difference is incredible. Everyone, including his rheumatologist and pediatricians, are amazed at the difference because they never thought it would happen. So the plea is to please approve that Enbrel be the first drug used and not only after other DMARDs."

DR. ABRAMSON: Okay. Thank you very much.

We're now going to move to a series of discussion questions that address the risk-benefit ratio of Enbrel and its proper place in these requested changes to the labeling. There are 12 questions, and we will try and spend about 10 minutes on each question.

The first is in the area of safety, and I'll just read the preamble. "In this trial and the original licensure trials, for patients with advanced RA, no differences were observed between Enbrel-treated and control patients with regard to serious infection. The occurrence of serious infections and deaths from infections among patients who received Enbrel in the post-marketing period resulted in additional language in the product label and the initiation of a randomized trial of Enbrel in patients with RA to assess infectious complications in a population at risk for potential risk factors. In addition, randomized controlled trials of Enbrel are underway to assess safety and efficacy and other indications."

The first question in the safety database category to the panel is, "Please comment on the adequacy of the completed and planned studies to assess the safety of Enbrel for long-term use in patients with early rheumatoid arthritis."

So would someone on the panel like to comment?

DR. HARRIS: May I?

DR. ABRAMSON: Yes, Dr. Harris.

DR. HARRIS: As I understand it, the study will be utilizing a thousand patients with comorbid conditions for four months. My issue is whether or not four months is an adequate period of time in which to do a study such as this, whether or not the risks might not exist for a longer period than four months.

DR. ABRAMSON: Dr. Siegel?

DR. JEFFREY SIEGEL: Yes. We also feel that four months may not be adequate to fully ascertain the risk of increased infections. This was a practical decision that was reached because it was felt that it would be very difficult to keep patients in the control arm of the trial longer than four months.

DR. ABRAMSON: Dr. Schwieterman?

DR. SCHWIETERMAN: Yes. Let me just add to Dr. Siegel's comments.

It's very difficult to know, of course, what an adequate length of trial is when you're reviewing the anecdotal post-marketing data, but of those events that we reviewed, a large majority of them, if there was a causal relationship, occurred relatively soon after the initiation of Enbrel, that is, within the four-month period, and so

based upon those observations and based upon Jeff's comments, that's how that study length was chosen.

DR. ABRAMSON: But given -- just to pick up on this -- given the denominator of post-marketing reporting, and if one assumes that the drug may not induce the infection but in someone who otherwise develops an infection prevents normal handling, one would then, in picking up Dr. Harris's point, want to know what the likelihood of events of infection would be in this population over four months, presuming it's not the drug that induces it but the natural history of the incidence of the event.

So how do you think about that? If you take a thousand diabetic patients and others, what's the likelihood that you're going to get a sepsis or some other event that gets complicated by therapy?

DR. JEFFREY SIEGEL: Unfortunately, we didn't have firm data to base these on. Some of the data that was used was data from congestive heart failure studies where the rate of infections has been quite high in some of the controlled studies.

DR. SCHWIETERMAN: I think your point is well taken. It's difficult to know with any certainty about how the study is powered or whether it's sensitive enough for these particular changes, and suffice it to say that

discussions occurred over actually the course of many months as to what kind of trial design, including much larger studies of a non-enriched population, enrichment studies and so forth, and based upon the analyses we did of the post-marketing data, albeit, you know, with full knowledge that those analyses would only give us a guess, a best guess as to what was going on, we felt that an enrichment study of these particular patients was the way to go, given the incidence of the events in these particular patients, and as to the power of the study, we could only do again a best guess as to what kind of signal we'd see with these groups.

DR. ABRAMSON: And Dr. Simon first.

DR. SIMON: In the context of doing an enrichment study, was thought given for such a short trial to be done only during those times of years where these individuals who are at risk are truly at risk for URI exposures, such as winter as opposed to summer?

One would have seen differences of infection rates, and are we concerned only with sepsis or are we concerned with upper respiratory tract infections that then are worsened while the patient is on an inhibitor of TNF-alpha, and then the other question, which I'm concerned about, relates to the LFT abnormalities, and the usage of this type of therapy in patients with known hep C disease.

There was an allusion to a study in hep C patients, hep C-infected patients, and could you comment on how you're looking at those kinds of chronic infections as relates to incidence of problems with superimposed TNF-alpha inhibitor therapy?

DR. SCHWIETERMAN: Well, let me comment on your first question first.

What drove our considerations for the trial design in the study was less the upper respiratory tract infections but more the serious AEs, including systemic inflammatory response syndrome relatively soon after the initiation of Enbrel, including hospitalization with serious infections, including quite dramatic Grade 4 infections from there, and consideration was given to all the kinds of adverse events that might be seen in those who would be collected.

But, principally, the study is designed to address the issue of catastrophic or very serious AEs. Undoubtedly, there are many, many questions remaining that could have been asked in this particular study, but given the gravity of our concerns about this, albeit with post-marketing data and a fair amount of uncertainty as to what to make of it all, we focused our attention on that.

DR. ABRAMSON: Okay. Dr. Katona?

DR. KATONA: Dr. Simon also asked about

hepatitis C. hepatitis C-positive patients are excluded from the trial. The hepatitis C population, that's a separate trial.

DR. GARRISON: I have one clarification about the hepatitis C population.

DR. ABRAMSON: Okay.

DR. GARRISON: There are seven patients in our clinical trials who have had hepatitis C and have been treated concurrently with Enbrel, very small numbers. None of those patients has had any problems with reaction or exacerbation of their hepatitis C.

DR. ABRAMSON: Okay. Thank you.

Dr. Katona, then Dr. Felson.

DR. KATONA: I think this is the other side of the coin for serious infections. I think the study getting the particular high-risk individuals for four months is going to tell us the short-term complications, but I would like to ask all the studies, what you presented for post-approval, have those all, including the European studies, are those all going to systematically be looking at all the complication rates? Because I believe that's the -- we really don't know how many years patients are going to be on Enbrel, and I think that's really the key for long-term, and we probably don't know all the data there is.

DR. GARRISON: When we were here last, we did

commit to following these patients in our long-term treatment trials for at least three years.

We have extended that to at least five years, and as long as sufficient numbers of patients stay in, we will continue to follow those patients. This is a very valuable source of data for us.

So yes, we're going to be following them for primarily significant events. Any hospitalization, malignancies. In the later portions of the studies, the more nuisance events are more difficult to collect. Patients get tired of reporting every cold that they've had, and I think that we have some pretty good data in our control trials that really very clearly shows the difference or no difference in rates of those kinds of infections, statistically-significant events, and we're following these patients for a very long time.

DR. ABRAMSON: Okay. I have a question about the European Registry. It was on one of your slides. Can you describe that?

DR. GARRISON: The European Registry is in almost its finalization form, and it's being conducted by Wyeth-Ayerst, and I don't have the particular details, but these patients again are going to be followed specifically for significant events, hospitalizations, serious infections, malignancies, autoimmune diseases, SLE, et

cetera.

DR. ABRAMSON: Is that via the licensing agency in Europe or is it --

DR. GARRISON: Yes.

DR. ABRAMSON: Okay. Other questions?

I have a question. I guess a lot of the difficulty that we have is in the potential for Type 2 errors that we're getting with follow-up, but how does one judge the three sepses in a septic joint in the study that we heard this morning with no sepses or bacteremias in the methotrexate? Is it a signal or not a signal?

I don't know that we can make a judgment, but can we assume that there is no difference in those groups? Can we make any statement, except that we need more follow-up or not? I'm just curious what other people think about that.

DR. JAY SIEGEL: Well, you know, what wasn't presented in any of the presentations that may bear somewhat on this, I think some of you may be aware of this, with Enbrel, the first indication that was studied, although not on the list of other studies, was in patients with full-blown active sepsis, and there was a significantly-higher mortality in the Enbrel arm than the other arm, and that underlies some of the ongoing concerns.

So we're looking at a database that is not

large enough to exclude effects and probably never will be, certainly in terms of long-term effects. We're probably going to, as with many drugs, you know, carry into the future some level of uncertainty as to the effects on things like malignancies or late infections, but I just wanted to point that out as a background for one of the reasons why these small trends that you're talking about are something that we've at least looked at carefully.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: I think we all grapple with that particular problem, particularly when asked to look at a new therapy to be used first line, when we don't understand a lot of the long-term toxicities.

Yet at the same time, we as rheumatologists have spent our lives using drugs that we don't really understand very much about their long-term toxicity, some of which have been very helpful, some of which have fallen by the wayside.

It is an iterative experience. Unfortunately, the regulatory environment doesn't appear to be able to help us with that too much at this point in time. Maybe perhaps the longer-term trials, the European Registry, will help us understand this better, although I'm a little concerned that the numbers may not be large enough to really give us the answer.

I'm particularly interested also in the malignancy issue as well as the sepsis issue, but I think that that should not preclude us from feeling very positive about this particular therapeutic intervention.

DR. JAY SIEGEL: Could I get a clarification? Because you made a note something about the regulatory environment isn't able to help us with this question.

Our question to you is, you know, what can or should be done? It may be that there are things that -- I'm not sure what you're presuming about the regulatory environment, but we would like to know what you all think should be done, so we could figure out what role we and Immunex and others can play in trying to get it done.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: Well, since I've been on this committee, I've had the opportunity to participate in discussions that are very similar to this.

We've heard ways that this committee has actually required other sponsors to actually create relatively small registries. I think that fundamentally, what we've learned is that we really need to move towards a way to study large groups of patients over a long period of time and to have large cohorts that are studied that way.

We have the opportunity to do that with governmental support if we could convene enough of it to

get it supported over time, so that we would have real registries, where all the patients with rheumatoid arthritis are followed or a great majority of them are followed for 10-20 years, and we can understand those kinds of implications.

I think the agency should take a leadership role in encouraging groups to do that. Recently, the American College of Rheumatology Board of Directors actually reiterated their belief that that's a very important thing for the government to support, the NIH to support, and it would be good that the agency saw its way towards thinking in that regard as well.

DR. ABRAMSON: Dr. Felson?

DR. FELSON: Yes. I'm going to reiterate a lot of what Lee just said, but I think it's especially an acute issue here where this is a compound where, unlike methotrexate or other drugs that were released or used in rheumatoid arthritis, we don't have any experience from other diseases and really don't have any sense of what its long-term effects are going to be, and I think the notion that this might be like other drugs recently approved by the FDA that had to be withdrawn later from the market because of an unanticipated but uncommon very severe problem is not unreasonable, and I think it would be nice to have real large-scale long-term -- the notion that the

company's going to follow these people for five years is very reassuring.

Frankly, the data presented here provide no reassurance that there's not an increased malignancy rate because the number of people followed is not sufficient to see an increased malignancy rate. The person-years analysis is misleading here. That event doesn't occur till three to five to 10 years later, and I think, you know, long-term large-scale observational data is absolutely critical.

I'm not sure it necessarily needs to be controlled data. I think sometimes, you know, controls that are already in the literature or controls that are created from other settings sometimes can help us figure it out, but I think there's a genuine concern here.

This is obviously, you know, something that's new and very helpful to patients. There's no question about that. But it's new, and its long-term biological effects are unknown, and I think that's real concerning.

DR. ABRAMSON: I think, just to add to this discussion, it is not just another drug that's been approved, and I think we need to come back to the hearing a year ago, because it is the first biological in this field.

There were relatively few patients studied at the time of approval, and that's, I think, important to

keep in mind compared to traditional pharmaceutical agents. So it's not just the numbers of patients, but it's the numbers and the time.

So this drug, because it's a very impressive drug and does all the dramatic things in many but not all patients, has a very important role, but we should keep in mind that it's the first of its kind that has a different level of numbers of people to follow.

I am concerned. I don't like data presented as patient-years when you only have small cohorts followed for a year or two. I think I agree with David. It's a bit misleading, and as Dr. Garrison said, you need four or five years to follow people if you're looking for a malignancy in this area, and so we don't have enough numbers and length of time, and that's the discomfort that I think is still there.

Dr. Simon?

DR. SIMON: And even when even a few malignant events are noted early on in an early RA trial, that makes me even more nervous.

We think of rheumatoid arthritis as a disease that has associated with a risk of lymphoproliferative disease over 30 years, not over three years, and although there is one Hodgkin's patient, and that certainly can happen spontaneously in all circumstances in anybody, it

just makes me a little concerned when I see data in patient-year, and I actually feel very uncomfortable that the sponsor has not acknowledged that at the get-go, that by expressing the data, it is almost the implication that in all of their trial data sets, that a patient-year expression is appropriate for this particular problem.

I do recognize that they have achieved ICH guidelines as of this present presentation, and I think that's wonderful, but at the same time, in this context of this kind of therapy, it may be 10 years before we can understand the implications of malignancy associated with chronic use of this agent or agents like it.

DR. ABRAMSON: So I think it's an appropriate time now to move to the second part, because I think we're also all impressed with the discovery and the bench-to-bedside work, and now the surveillance that the sponsor is providing, working with the FDA. So I think everybody's moving along in a very, you know, exemplary way.

The issue then becomes the second question here. "Should the sponsor conduct additional studies beyond the usual post-marketing surveillance to further assess the safety of Enbrel in patients with early RA? If so, please comment on the kinds of studies that would be informative."

Dr. Pucino?

DR. PUCINO: Yes. I think it would be helpful not to just know numbers but the pathogenesis behind why people are getting DVT, why are people seroconverting to positive antidouble-stranded DNAs, and why are people developing malignancies, and to try and focus on the why and not just that it occurs.

DR. ABRAMSON: Right. Assuming these are validated observations.

Dr. Katona?

DR. KATONA: This is a question for Immunex, and I'm just kind of looking forward to the future of five-10 years from now, if there are patients with malignancies or some unforeseen events, and at that point, we might come to the conclusion that we completely have to abandon our treatment which was very useful for very many patients.

Has any thought gone into using Enbrel as an inductive therapy, like for a half a year or a year or a year and a half, and follow those patients along, switching them to another therapy at that point when the disease is well-controlled and collecting long-term data maybe on those patients along with patients long-term on Enbrel?

DR. GARRISON: We have not conducted a study of that design. It's something that has been suggested to us.

We have a large number of studies that we're trying to conduct, and I think that it is one that will be

done, whether it's by Immunex or by the rheumatology community.

One other point, if I may make one point, about the malignancies, is that we have looked very carefully at each of these cases, and although patients in this trial had RA of short duration, many of them were not young people. Many of them had multiple years of smoking history, et cetera, et cetera, other risk factors that would make you not dismiss their malignancy, and I'm not saying that at all, but at least not make you think, well, this is something very odd that's happening in this person.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: I also wondered, taking Frank's lead here, we've not really talked a lot about the observation about the absolute neutrophil count, and that didn't come up in the discussion of the sepsis issue.

But I'm not entirely sure I understand the biology of that at all, and obviously it's a very important issue in the question of sepsis and response both to minor infections as well as serious ones. That's clearly an area that we need to further understand since it really stands out as something unique to this kind of therapy, and why that would happen is unclear.

DR. ABRAMSON: Right. Were there other cell lines, like platelets, or any other -- in terms of the

sponsor? In people who were neutropenic, was there a drop even in the normal range --

DR. GARRISON: No.

DR. ABRAMSON: -- of the platelet count or something?

DR. GARRISON: No. There was no thrombopenia at all.

Can I show a slide?

DR. ABRAMSON: Sure.

DR. GARRISON: Okay. Slide up.

This does go into a little bit greater detail about the ANCs that were seen in the trial. You know, we did measure these cell counts very frequently during the study, and we've just shown any grade as well as the specific grades that are associated.

As you can see, most of these were Grade 1, which is at a level of 1,500 to 1,999 cells per cubic millimeter, which I think may occur in the setting of RA transiently in and of itself. Not to dismiss that, but again looking again at more severe levels of neutropenia, there were no significant differences. I mean, 1, 3 and 3 Grade 2, and 1, 1 and 1 3 in this trial.

If we looked at our placebo-control trial, just one more, the differences were not seen there in Year 2 in the ERA trial. There were no differences among the groups.

If we look at the Phase III placebo-control trial, where we did have a placebo, we did not see anything reflecting this pattern at all.

DR. ABRAMSON: Thank you.

Dr. Brandt?

DR. BRANDT: You pointed out earlier that the cases of thrombosis were not associated with the presence of anticardiolipin antibodies.

Can we say the same thing about the episodes of sepsis not being associated with cytopenias? Do you have that information?

DR. SILVER: In the ERA patient, the one patient with sepsis, was in the setting of a pneumonia. That patient did not have a low neutrophil count. The bacteriemia is different from sepsis, and the patient was not hypotensive, had a positive blood culture after someone needled a cyst, and the patient was septic arthritis. I don't know for sure, but I think that patient also did not have a low neutrophil count.

When we looked at these patients with low neutrophil counts, we looked at over their whole time had they had any serious infection, and none of them had.

DR. ABRAMSON: Dr. Harris, and then Dr. Simon, and then I'm going to go around and ask each panel member if there's one area that they'd like to see in response to

this question that needs further study.

Dr. Harris?

DR. HARRIS: I'll ask a question. There's no reason a priori, of course, if the thrombosis story is indeed something that pans out, that it need be antibody-related, and certainly the molecule itself could perhaps activate endothelial cells or platelets in some way and be itself prothrombotic, and I was wondering whether or not there's any in vitro or other data to suggest that.

DR. FINCK: I don't know of a lot of data, but there was some data that looked at -- I think the author was Seffarini -- the presence of TNF actually in increasing coagulation parameters. So that would be opposite, and that's the only data that I'm aware of.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: Not to beat a dead horse about this absolute neutrophil count problem, but I'm a little uncomfortable with the explanation that's just been presented in that we do know of patients that have particular syndromes associated with rheumatoid arthritis who develop very profound neutropenia, but these were not these patients, and this was a longer trial than the Phase III trial, and therefore I'm a little concerned that perhaps we're beginning to see a long-term event taking place on exposure, and because Dr. Garrison presented some

two-year data, I wondered in the two-year data set whether there was any incidence of absolute neutrophil counts as well or whether that incidence increased in that circumstance.

DR. GARRISON: In the long-term open-label trials, we've evaluated these people hematologically, serially, and we haven't had any neutropenia that's been associated of this pattern at all.

DR. ABRAMSON: Thank you.

So in terms of this question, now we've heard that there's a high-risk four-month study, people at high risk for infection. There's a European Registry being planned. There's going to be follow-up of your clinical trials for three to five years, and I guess what I'd like to do is just ask the panel members if there's one or two things in the context of those things or additional things they'd recommend that they want to have tracked or have some concern about.

Dr. Siegel?

DR. JAY SIEGEL: Could I also supplement that question?

Since I've heard a number of panelists emphasize the importance of long-term data, and at least one laud five-year follow-up and another says we need more than five-year follow-up, I think Immunex -- I remember

although they've presented patient-year data, they noted that first, as well, that you really need longer data to look at that.

So the question is, you know, five years is better than three, but where should we get --

DR. ABRAMSON: I don't know. You need people who are maybe more expert in latency and things like that.

We as rheumatologists who are old enough have had the experience with Wegener's granulomatosis -- I guess it was in the mid-1970s, whatever -- an incurable disease was made better by Cytoxan, and at the five-year follow-up, there was, what, 20 percent lymphomas, lymphoproliferative disease, et cetera, as well as bladder cancer.

You know, for us older people, that's in the back of our minds. I don't know that they're two different drugs, but there is this little bit of a signal, and I think that's the concern, in terms of being more aggressive in its use as a question.

It's obviously a terrific drug for many, many people, but that's the anecdote.

So Frank?

DR. PUCINO: Again, more information on pathogenesis of these things if they are proven valid. Also being a little bit more proactive instead of waiting till someone develops lupus as we know with other anti-TNF

therapy has developed, to be serially monitoring these things.

DR. FELSON: I'll dredge up another example that's in the opposite direction actually with methotrexate and liver problems, and I think we're all worried about long-term liver complications from methotrexate, and it really wasn't until 10-year follow-up studies came out from Mike Weinblatt and Joel Kremer that our concerns were generally assuaged.

They weren't huge studies, but they had enough follow-up that they basically excluded the possibility of frequent cirrhosis and that was very helpful, and I would think that these are rare events. So small numbers of patients followed up for 10 years is not going to be all that helpful. We need bigger numbers, but I would ask the company to begin to project that.

I mean, this is a very popular treatment. It's going to be used by thousands of patients for long periods of time, assuming, you know, a lot of things that we've heard in evidence today, and I don't think it's so far-fetched to think that they could continue following these patients to figure out whether they develop malignancies, and what the rates of that are.

DR. KATONA: I think at this point, it's very difficult to say too many new things, but I would like to

look at this from the patient's perspective and more like asking the regulatory agency just we really have to make sure that the patients understand that we really do not know exactly what is going to happen five-10-15-20-25 years from now, and especially speaking from the pediatric community, maybe 70 years from now.

So I think until we're honest about it, and both Immunex, other companies, as well as we, the rheumatology community, collecting the data, that's all I could think of.

DR. SIMON: I'd like to actually generate my comments more to the agency than to the individual companies.

I don't think it's fair to ask the company to invest in what really is required, which I believe that the agency can take a leadership role and a bully pulpit role in getting the community to develop long-term observational trials, outcome trials, of the use of not only TNF-alpha inhibitors but other drugs as well in the context of the treatment of rheumatoid arthritis.

As David had alluded to, the positive aspects of understanding the liver toxicity of methotrexate also led to a far better understanding of the incidence of lymphoproliferative disease in the treatment of patients with methotrexate, and only by doing those kinds of 10- to

20-year studies will we really understand the incidence of that and its effect, and I believe the agency has a major opportunity here to play a very major leadership role in getting the government to truly sponsor and support so that the rheumatology community and others can study the incidence of problems in these patients.

MS. MALONE: I agree with both what Lee and Ildy have said. I think there is the need for large-scale long-term follow-up.

Also, I think in this follow-up, we need to take into consideration that rheumatoid arthritis is not happening in isolation, that as these people age, other things are happening to them, and, you know, what the interplay is with this drug.

It all sounds almost too good to be true, you know, and I personally know people who are on the drug, and it's been miraculous, miraculous, but I think, like Ildy said, that there has to be the education on the part of the pharmaceutical with the doctors and the doctors to the patient that the future is unknown.

DR. BRANDT: Yes. I think we've seen some very impressive positive results here, and I can certainly understand the enthusiasm, but as I think everybody has said, we just don't have data that permit conclusions over long-term usage, and we need those both from the standpoint

of infection and the standpoint of malignancy in sufficient numbers of people to be able to answer these questions.

It takes time, and it's going to take money, but I think it's essential.

DR. ABRAMSON: So I would agree. I think the good news is we're not discussing licensing this drug or not. It's already licensed, and so the issues are different, and if we can educate doctors and get access to patients of good care, what we're really talking about is delaying three months the use of methotrexate, for example, until this drug were available for patients. So the issue of safety given its numbers and experience, I think, is still out there.

What we saw this morning was encouraging, and I still think we need more data as we're saying on sepsis and tumors. I think the LFTs have to be tracked a little more closely. As Lee brought up early this morning, I don't know whether that 20 percent AST or ALT --

DR. SIMON: ALT.

DR. ABRAMSON: ALT elevation was a real signal or not, but I think it should be kind of looked at in these studies.

I think the use in hepatitis C, a lot of our patients are carriers of hepatitis C, and that's an unknown area. I don't say that's a new study, but I think at some

point, we ought to start looking at opening up the use of this drug because those people are treated with interferon which can exacerbate their arthritis. So they're a real difficult patient population to treat for the clinicians, and if this drug were good, I think that's a useful area.

I share Dr. Harris's concern that the four-month high-risk trial may not be apparent to really see signal of infections that are going to happen in these patients that then get worsened by being on drug.

So those are my comments.

Dr. Harris?

DR. HARRIS: Well, my comments are, again, just urging careful monitoring, and I feel that the burden is on the FDA to do exactly that, which is to monitor carefully. I'm sure you do that anyway, but I think that is the important thing, and then the other point that was made is that patients themselves, at least there should be some sort of warning about not knowing the long-term effects, and indeed, I am going to add one other story, of course, corticoid steroids in the early '50s.

Of course, rheumatoid arthritis was the disease in which this was the miracle that didn't work 10 years later. Hopefully that won't be the case here.

DR. JAY SIEGEL: Just to be clear on that issue, we monitor in the sense that we monitor reports that

come in from the community which are, as we've seen in this case, extremely difficult to make determinations about regarding incidents relative to background in areas such as we're talking about, infections and malignancy, except when there are very strong signals.

So if there is a need for a more reliable source of data, then that would need to come from the planned either controlled trials or cohort studies, and what we're discussing now in fact is which of those we should be asking the sponsor to conduct at this point in time.

DR. ABRAMSON: Janet?

DR. ELASHOFF: It definitely seems clear that one needs long-term studies which are better than post-marketing surveillance studies. Whether you actually need a control or whether you just need careful follow-up of, I think, generally multiple people treated under multiple conditions because then at least you can compare within the data set itself. Although you don't necessarily have a great comparison, at least you have some comparison, whereas post-marketing surveillance, you typically don't really even know the denominator, let alone what would go on in other circumstances.

DR. ABRAMSON: And an additional thought in terms of who should bear the burden of this, I think the

NIH could play a role here, too.

I know they're looking at targeted studies that are hard to fund and some surveillance, I think, would be worth talking to them as well.

Kent?

DR. JOHNSON: Let me just interrupt for two seconds.

Just to expand the discussion a little bit, there are international thoughts on this, too, as a lot of people in this room know. I think it's quite obvious to everybody here that our post-marketing system is incredibly limited, as are post-marketing systems for most other countries in the world.

Whether the EU is going to start some formal requirement, I would love to see that happen. I would love to see the FDA kick in, also. There's a group called OMERACT, which is just a very ad hoc organization, that's been thinking about long-term databases in rheumatoid arthritis for exactly this sort of thing.

The big conceptual challenge is even if you do a 10-year study, and you find, you know, a handful of lymphomas, what does that mean compared to background? How do you make a rigorous comparison? Do you need a control? Do you need matched controls?

We're never going to get 20 randomization

studies, but you could deal with the control problem, although it's very tricky, you know, from a complexity point of view in cohort studies.

But I think the greater issue is how to get this organizationally going. There's three centers right now, the Stanford Center, Manchester and Sweden, who have at least on a preliminary basis thought about at least establishing a common database which is the beginning for something like this.

The whole other dimension, and nobody's mentioned it, although the patients, you know, would be interested in this, what happens to efficacy long term, because really you want to make a risk-benefit judgment for a 10-year proposition, and you need some efficacy data which is tricky to ask the companies to collect, although it hasn't hesitated me from doing that.

DR. ABRAMSON: Dr. Brandt?

DR. BRANDT: I'm going to save mine for later.

DR. ABRAMSON: Dr. Paulus, would you like to make a comment?

DR. PAULUS: Obviously, there's a lot of intellectual and emotional interest and support for truly long-term collection of data in an observational cohort-type study over a generation or longer, but to do that, you really need sustained long-term commitment and money, and I

think that one model for funding something like this is the Orphan Drug Program, which is really very successful and is a collaborative effort between industry and the agency that has legal authorization to go on for as long as necessary and that may be the way to go with this.

DR. ABRAMSON: I think that's a very key point, that this shouldn't be the burden of the individual sponsor of an individual drug at some point, because we're going to keep seeing new drugs come out between the industry, the FDA and the NIH.

Perhaps there ought to be some way to designate certain of these new products for long-term follow-up.

Okay. So on Questions A and B, in terms of the agency, are there other issues that you want addressed there?

DR. SCHWIETERMAN: I just want to be clear. This has been a valuable discussion.

But are there any specific studies that might be needed, and perhaps before we answer that question, Dr. Abramson, you may want to delay that until we get done with the efficacy discussion, but since obviously this is an issue related to the overall risk-benefit.

DR. JAY SIEGEL: And am I correct in understanding -- maybe I got heard wrong. But the sense of this committee is that we should not require this company

to address the long-term needs; rather, we should spend our efforts urging the NIH to do it?

DR. ABRAMSON: No, no.

DR. JAY SIEGEL: That's what I thought I heard lots of people say.

DR. ABRAMSON: No. I think you were hearing options. I think I'll take a crack at it.

What you heard from the committee is that we need more long-term data, that you're doing with the company a lot of very important things to address that.

I think there's a sense that it may not be coming up to the necessary level perhaps, the four-month issue and the infection we talked about, that maybe that needs to be extended, just as an example.

But I think in the bigger picture, the long-term, big picture is that the agency and the corporations and NIH have to look at this as a generic problem.

I think for this particular issue, beefing up what already sounds like it's being done, it sounds like we're very much on the right track here with the European Registry, the five-year clinical trial follow-up, and this high-risk group, and then backing away from being able to make any comment about tumors just yet, based on the one- or two-year period.

I don't think it's fair to make a presentation

that there's no increased risk of tumor because we have 25,000 patient-years of experience. We have one year of experience in 25,000 people. That's all we have.

DR. SCHWIETERMAN: Let me just add, if there are no more comments, I think it's sound advice we're hearing, and the agency has actually heard this before from this committee, and without getting into the policy that we're having for the development of rheumatological agents, given that this is a rapidly-developing field, and obviously the standard of care and the needs of the patient are changing, our requirements simultaneously are changing, and so I just want to reassure the committee that this is not a static thing, that we recognize the points being made and have actually begun to engage sponsors in high number of patient trials and so forth.

DR. ABRAMSON: And remember, we're not talking about withdrawing this drug or approving this drug.

Any other comments?

(No response.)

DR. ABRAMSON: Okay. So let's go on to Clinical Measures. "Rheumatoid arthritis is a chronic disease with symptoms that wax and wane over time. Drug effect can be assessed in different ways. The measurement that captures the entire experience over the duration of the trial, and that potentially discriminates small degrees

of improvement, such as the integrated ACRn, has the advantage that it incorporates all the trial data.

Alternatively, measures, such as ACR20, may better reflect a meaningful clinical response, and there is more experience validating this as a measure of clinical benefit compared to the ACRn.

Finally, endpoints that are measures of response status at the end of the trial may better reflect the likelihood of a durable response and thus be more clinically meaningful.

In this trial, Enbrel effects on ACR were detected earlier than methotrexate, but the differences at the end of the study were less marked."

I'm going to ask David Felson to first comment on the Question A here.

"Please comment on the use of ACRn area under the curve as the primary measure of clinical benefit."

DR. FELSON: I think this was a well-designed and well-thought-out trial. Let me start off by saying that. I was personally very impressed at how the data were presented and how they were planned.

I got the sense that there are two ways of evaluating the outcome in the efficacy of the analysis that were used here, and I think we need to separate them.

One is ACRn, and the other is area under the

curve, and what generated the power that was seen was primarily area under the curve, which can be used also for ACR20. It almost always generates more power to average effects over time in people than it does to take one landmark point in time, and symptomatic of that was the comment I think Jeff or someone else made that when ACR20 area under the curve was looked at, it also showed highly-significant differences between Enbrel and methotrexate, suggesting to me that that was the reason that there was more discriminate validity here, was because the area under the curve analysis was used, which is a thoughtful and appropriate way of analyzing data which may not show as much precision and power at any given point in time. So I think the notion that ACR20 might not be as good as ACRn is -- I don't know that this trial speaks to that.

I should just comment that ACRn turns out to revolve around one measure, if you think about it. So what happens is a patient improves by five out of seven measures, and then the ACRn is defined as the measure among those in which the patient improves the least.

Okay. So it's dependent on one single measure, not on a panoply of measures, although to get there, the patient actually has to improve on a panoply of measures, and that is not as statistically powerful as developing, say, an index measure, and therefore it would be expected

that if you wanted to maximize discriminate validity, you wouldn't use ACR20, you wouldn't use ACRn, you'd just use an index measure, and that's actually in the ACR Committee development work that the FDA was involved in, and that's what the statisticians all wanted to do, because they knew it would maximize power.

The trouble with an index measure, and somewhat the trouble with ACRn, is mentioned here in this paragraph, which is that there are a lot of other elements to the process that we went through. One was to try to figure out what's a minimal clinically-meaningful improvement, and that was done with surveys of rheumatologists testing out patient improvement, and that threshold of greater or equal to ACR20 in multiple different outcome measures was arrived at after that other element was decided upon, okay, meaning that that greater or equal to 20 percent isn't just chosen because it provides the best discriminate validity. It turns out its discriminate validity is quite good, but it's also there because it sort of represents a minimum threshold level above which patients seem to have improved, clinically improved.

And the other big advantage right now of ACR20, and it's not necessarily a reason to continue to use it, but it turns out to be a big advantage, is that it's being reported by everybody. So if you look at the presentation

that the Immunex folks made and the FDA made, there were explicit comparisons right off the bat with ACR20 rates in other trials, other drugs, methotrexate and other -- I mean, I can tell you there are lots of such comparisons.

It's a very valuable benchmark now because it's being widely reported. So I would think that -- you know, could other ways of evaluating efficacy be used, might they work better in terms of discriminating between active treatment and control? Yes, you bet they might work better.

Does this work pretty well? Yes, it works pretty well, based on a lot of different analyses of different data from different data sets.

I would suggest that it's a very reasonable way of testing efficacy, and that it provides a nice standard that we can all go to a lot.

One other comment about the results presented, and this paragraph also comments on it, I think, very perceptively, which is that in my reading of the ACRn analysis and the area under the curve analysis that was done in this trial, that the difference in AUCs is generated by the fact that the Enbrel patients respond earlier than methotrexate patients.

It's not necessarily based on the fact that there's any important difference in the ultimate response

rates of Enbrel and methotrexate, and I think that's a distinction that we need to keep in our mind's eye as we look at this trial.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: I also agree this is a very well-designed trial, and for those who don't know, I'm not a fan of methotrexate, but I take a little issue about the earlier response issue, because, in fact, when you think about it, they were patients who were underdosed at the beginning with methotrexate, based on safety and other issues, and they may have been overdosed with methotrexate later on in the trial, showing equivalency or lack of difference in response between the two, until you did an ACRn.

So I'm a little bothered by some of the claims that you would get rapid response which may be seen with methotrexate as well, although the incidence of three patients with interstitial pneumonitis augurs poorly for the use of high-dose methotrexate.

On the other hand, we've all seen that more methotrexate is used all the time, and it's not uncommon in my practice to start off patients well above the 7.5 milligram point and then us putting patients at greater risk.

Thus, I still am confused in the discussion

that David just gave, in that we saw improvement with the ACRn across all parameters at all time points, but yet when you look at the ACR20, there was no difference after six months to a year between the two.

Which one do we put more weight on?

DR. FELSON: I'm not sure. I guess I'd defer to the company or to Jeff or someone who's analyzed these data. I didn't see them do an analysis of efficacy parameters between six and 12 months. It looked like the radiographic parameter changes weren't different between the two groups, but, I mean, the differences were generated by that early zero- to six-month curve primarily, I mean, in almost every one of those outcomes.

DR. ABRAMSON: Can someone from Immunex address that?

DR. JAY SIEGEL: It is somewhat comforting to note, I guess, in our analyses that if you look at the various ACR curves or the various radiographic curves that on almost any endpoint, Enbrel at 12 months had a point estimate that was somewhat better than methotrexate, but I think it would be correct to generalize across them, although there may be some exceptions that, if you look at specific points in time in general, you see significant differences in the first several months, and then in the last half year, you see still a separation but no

significant difference.

DR. FINCK: I'd just like to add that the endpoint of area under the curve for ACRn was the prospectively-defined endpoint. It wasn't used after the fact to make the two drugs look different.

We did prospectively define it as the prospective endpoint because we did want to try and follow FDA guidelines that recommended that area under the curve might be a better way or at least over time might be a preferable.

I don't think we really had seen a lot of area under the curve or over time analyses except in the European data, which is very impressive. They use the disease activity score over time.

We agree that there is not a significant difference at a single time point at the end of six months or 12 months, but the rapidity of response with Enbrel is an important feature of Enbrel and needs to be taken into consideration, and we did give methotrexate a reasonably fast onset, so that it could have its best performance.

Actually, in clinical practice, it may have a much slower onset, and the difference would be even greater, but I would like to show one slide because I think that it shows you how powerful the ACRn under the curve was, and that is, if you look at weeks at ACR20, weeks at

ACR50, weeks at ACR70, which have been used in other trials, there's statistical difference, in fact very impressive statistical difference, between Enbrel 25 milligrams and methotrexate, and also, if you look at the DAS, which is a validated index that's used as area under the curve or has been reported as area under the curve, it also shows a very high statistical performance between 25 and methotrexate, and when we did a correlation coefficient between the area under the curve for the DAS and the ACRn, the correlation coefficient was .8.

So these two measures correlate very, very well, and you can also do area under the curve for any of the individual ACR criteria, and Enbrel 25 milligrams performs better than methotrexate with the exception of tender joint count which approached significance but did not go over significance.

So I think you have a choice, but we did prospectively define, and again I'd like to remind the committee we're asking for efficacy, not superiority, over methotrexate.

DR. ABRAMSON: Right. While you have that slide up, and picking up on Dr. Felson's point, how much could that be attributed to the earlier response?

If you're dose escalating methotrexate, so the first month or so, you're lagging behind in getting a

therapeutic effect, how much -- it's just understanding how the data is presented.

DR. FINCK: We also want to show that the responses -- we're looking for a slide comparing the Phase III results in placebo-controlled trials to what we saw with Enbrel in this trial, in the early RA trial, compared to methotrexate, and I don't know if we're able to find that.

But many of you do remember these, that in our earlier trials, we saw similar ACR response rates at the prospectively-defined endpoints of the trial that we saw in the ERA trial.

So we didn't feel that we in this trial had to actually show that Enbrel was effective against placebo. We had shown that, and that it was important to show that it was effective and at least as effective as --

DR. ABRAMSON: But that wasn't my question, though.

DR. GARRISON: And we do have everything.

DR. ABRAMSON: Dr. Brandt has a question.

DR. BRANDT: You have about one out of three patients who doesn't hit ACR20.

What have you done to compare the responders with the non-responders, and what have you learned about the differences between people who respond and people who

don't?

DR. FINCK: We've actually looked at this.

Can I have the slide up? We've looked at ACR responders and non-responders using the ACR20 criteria as a landmark analysis and looked at not only total Sharp score but with erosion score and clinical response, but in this case, if you look at the radiographic results, you can see that there's really not a clear pattern.

There are responders and non-responders who have very little change on their total Sharp score and on their erosion scores, and although the Sharp scores tend to go up in the methotrexate and in the lower Enbrel group, they go down, there's really not a correlation per se.

Can I have the one -- I think it's 4. That's it. If I could have this up, we did find a correlation between patients who had the best clinical response with patients who had the least radiographic progression but not when we looked with ia landmark analysis.

When we looked at it over time, the best correlation was with area under the curve for improvement in CRP with a correlation of .45, which is similar to what's been reported in the literature, and every other measurement that we looked at as an area over time or improvement over time, we saw that those patients, the better their response, the least their x-ray progression.

DR. BRANDT: I was wondering about predictors at the outset.

DR. FINCK: Right. We didn't find -- you mean in terms of the out -- I'm sorry.

DR. BRANDT: Are there any differences at baseline that you might use to predict responders and differentiate them from non-responders?

DR. FINCK: No, we didn't find any baseline predictors that would have suggested we could have sorted them out.

DR. ABRAMSON: Dr. Katona?

DR. KATONA: A follow-up question on the very same issue.

In the briefing document, there was one figure that the age 60 and less than 60 and more was compared, and these were looking at erosion scores, and that was really the only figure in which Enbrel performed worse than methotrexate.

So the question is, was the group which was about, if I remember, 25 percent of the patients, more than 60 years of age, different in any way response rate or complication rate different from the others?

DR. FINCK: First, I'd like to show the odds ratio for the age less than 60, greater than 60, if I have that up.

As you can see, to the right of the blue bar -- for this, it would be that if it's to the right of the blue bar, it means that they had better response on Enbrel, and to the left of the bar means that the response was better on methotrexate.

Most of the patients were under the age of 60. So we get into talking about very small numbers here, but you'll also see that those confidence intervals overlap that bar or that blue line. So I don't think you can make a statement that anyone over the age of 60 would not have an effect from Enbrel.

DR. ELASHOFF: I have a brief comment on this.

Looking quickly to the FDA analyses, from what it looks like is that for the Enbrel group, you can't do much by any of the baseline predictors that they looked at, although perhaps some of them worked for the methotrexate group as predicting more or less response.

DR. ABRAMSON: First, Dr. Simon, and then Ms. Malone.

DR. SIMON: I just want to go back one more second to the minimally clinically-important differences because both of those issues seem to be growing in importance as we're looking more and more at this data.

I'd like to reiterate that again this is a very good study, and it has very good data in it, but a little

bit of a problem is, is that we don't even know yet whether these measurable differences in x-ray change are important clinically.

We think they might be. We still don't know, but, more importantly, I wonder if again I could ask David to comment. Since the ACR20 has built in kind of a minimally clinically-important implication in its measurement, the ACRn does not. How does then one interpret the change as being between methotrexate and Enbrel as being important or not important, although statistically important?

DR. FELSON: Well, you can't make a judgment about whether it's clinically important if you use the ACRn because there's no guideline as to what particular ACRn difference might be characterized as clinically important.

I mean, the potential advantage of this is that it might be able, because it's data-based and data-driven, to have a little more discriminate capability, although because it's derived from one measure rather than all seven measures, it's not very likely to be. But clinically-important improvement is not determinable here from this measure.

DR. SIMON: Can I just make one more comment about that? Sometimes things get brought up at this committee and to the agency, and then other companies in

the audience or elsewhere then jump on to the bandwagon because they see a successful measure that gets then approved or voted on in certain ways.

I would like to reiterate that that's a very important point, that if you don't have any defined minimally-important issue that you can then apply to the measurement, it becomes very difficult to understand how to think about that in the care of a patient, and I'd like to urge people before they start to use the ACRn regularly, that they remember that we don't know what it means and what the changes might or might not mean as it relates to the progression of disease or how the patient functions over time.

DR. JAY SIEGEL: I have no problem with that advice, but I would like to point out that there's a difference, and when you talk about what's minimally-clinically important, there's a difference when you're talking about an individual patient level and a study level.

One of the factors that goes into a determination that 20 percent improvement is meaningful is how much improvement it is to make a life difference in the patient, but another factor that goes in often, and I'm not a rheumatologist, that often goes into these cut points is, well, you know from experience that if somebody is 10 or 15

percent better, then the next time you see them, they'll be maybe 10 or 15 percent worse, and so you don't know if that's a real change.

If that's a factor, that's not the same when you're looking at a 10 or 15 percent improvement over a large number of people that's statistically significant. So that's just something to bear in mind.

DR. ABRAMSON: Leona, please.

MS. MALONE: This is sort of a basic question from the patient's viewpoint.

If you're not showing that the Enbrel is superior to methotrexate, why would a patient new to the disease go ahead and take Enbrel as opposed to methotrexate? I mean, that's basic. It's why. Methotrexate's been around a little bit. There's a little more data on it.

What would be a deciding factor? I'm a patient. I don't know what to do.

DR. JAY SIEGEL: Let me answer that question first because I don't want to answer it from the marketing perspective but from the legal perspective and just to mention two things.

One is that our law requires that a drug be safe and effective. There's nothing in our law that requires that it be as effective as other drugs that are

out there. So a lot of hypertensive medications, antibiotics, whatever they are, get approvals that haven't shown themselves to be superior to other drugs.

Just from the regulatory point of view, it's important to note that.

From a drug development point of view, it's important to note that there are many reasons why a drug which is equivalent in efficacy may be preferable. It may have a better safety profile. It may cause cost competition. It may be more effective in some subsets of patients. It may be more effective in patients who fail the other one or it offers different therapeutic strategies and regimens.

So there are reasons behind the regulatory approach that allows additional effective drugs to be approved, but that's not addressing your question as to why one would choose the product.

MS. MALONE: No.

DR. ABRAMSON: Let me address that.

MS. MALONE: I understand that. I understand that, and I know that the need for, you know, a lot of different medications in the same class is because sometimes one will work, one will not.

But what would make me want to take this initially?

DR. ABRAMSON: In fairness, there are, as we've heard during the public hearing, people who have very dramatic and extraordinary responses in the short term to this drug. So that it's hard even to do a double-blind study sometimes because people get so much better, and I think that is the issue.

Now, the data over time then you see, over six and 12 months, the differences tend to become closer, and so that that immediate dramatic effect arguably tends to diminish.

Now, there may be many people, and I'm sure the patients here today will tell you that this effect can be sustained and extraordinary. So I think that's what we're talking about, but really what's on the table today is does waiting three months for methotrexate to work compromise you from getting that effect?

It's not like you can wait 20 years with rheumatoid arthritis before you can get to this drug as some of the people we heard from today had to do. The drug's terrific. It's on the market.

The question that we're discussing today, if many people just come together at three months, and we don't have enough safety data yet perhaps, that's the question.

Now, the other thing is that when you look at

the ACR50s and 70s and don't talk about individual anecdotal experiences, you know, you tend to see curves that are very comparable with many of our drugs.

So it's not as if a 100 percent are getting better on this drug and only 50 percent on our other drugs.

Lee?

DR. SIMON: Well, that extension really leads to what's minimally clinically important, and what are the differences, and that's why this is such a difficult question, and your point about individual responses versus group responses is really critical.

Unfortunately, clinical trials are group responses, and they're designed and done for a regulatory issue, of approval, based on the law that you so eloquently described.

The problem, of course, is that doesn't answer the questions that we need, which goes back to the original discussion, and the problem is, is that often what gets done in this business of regulatory discussion is not the same thing as determining what is minimally clinically useful or important, but that's what Dr. Abramson is referring to, and that's what goes into the different decision of which drug to choose at which point in time.

DR. ABRAMSON: Okay. We'll do one last comment, and then we'll go down through the questions.

David?

DR. FELSON: I actually wanted to make a comment that was derived from looking at some of the slides and thinking about this a little.

We've published data suggesting that especially for methotrexate, that response rates diminish with disease duration quite dramatically, so that if you start drug early in disease, you get a very high response rate. If you start drug later in disease, probably later patients also represent patients who haven't necessarily done well with earlier treatments, you respond less.

In C-83 of the sponsor's presentation, there's a histogram of ACR response rates across their different studies, and I think their original studies wee salvage patients, like all RA studies start with, patients with quite long disease duration, and what you notice here is not that curve, okay, meaning that response rates don't vary by disease duration.

The DMARD failures, Phase II-Phase III, failures methotrexate and Enbrel, and please, company, correct me if I'm wrong here, were all studies done in patients whose mean disease duration at baseline was something like nine to 10 years. In one of the cases, I think it was five years.

DR. GARRISON: Eleven years.

DR. FELSON: Eleven years. Fair enough.

Now, the distinction is that methotrexate, which is depicted also on one of these histograms, has a dramatically-better effect early in disease than in later disease.

So the response rates to methotrexate in this trial was 65 percent. In the other big early disease duration trial, which is a comparative trial of methotrexate and auranofin that Mike Weinblatt did, it was 68 percent, okay, as opposed to methotrexate treatment later in disease, which has much lower response rates, 35 to 40 percent.

So one of the arguments -- and to bring this up, we're sort of talking about -- it gets at the comment you made, Steve, of are we really holding back something that's helping patients?

Frankly, the data suggest that people with early disease respond to just about everything, and that it's only in later disease that the response rates for other things start to tail off, and this really assumes -- so, you notice that in order for them to demonstrate a statistical significance between measures which have been easily able to detect significance between Enbrel and other drugs and other studies, they had to come up with an area under the curve special analysis. The ACR20 repeated

measure didn't necessarily do it, and that's because the differences were really small, okay, and that's because methotrexate works well in early disease.

Okay. This treatment has its greatest marginal effect on efficacy and greatest help for patients later in disease, not earlier in disease.

DR. ABRAMSON: But not to be denied early.

Just want to know if Drs. Garrison or Finck want to comment on what Dr. Felson said.

DR. GARRISON: Well, I think you're right, that we have very good consistency of our results in multiple disease durations, kids, adults, elderly.

We tried very hard in this trial to design it so that methotrexate would work very well, and we did do sort of a look at most of the physicians who were involved in this trial, and they were marginally uncomfortable with how aggressively we were dosing methotrexate three years ago.

So they would not have wanted to start methotrexate at the levels that you're starting at in your practice, Lee, and I think that the rapidity of response is important to people who have chronic pain, and what we're asking for here is not that all physicians use Enbrel first in treating every RA patient.

What we're asking is that you be allowed to

have the option to use this first in a patient that you think that Enbrel is the treatment you think is best for that person.

DR. ABRAMSON: Why don't we move on to B and C together, and I'm going to read it but ask again Dr. Felson, who has the most experience in this, to make the first comment.

So "if approved for the proposed indication, to what extent should the label for Enbrel reflect other measures of clinical benefit, including landmark analyses of ACR20 at six and 12 months, and to what extent should the label emphasize higher degrees of response, including ACR50 or 70?"

DR. FELSON: I think that the label ought to have as much information that's clinically useful as possible, and I think those are useful pieces of clinical information, so I would think that both B and C, the answer, I think, is yes.

DR. ABRAMSON: So the question, when I read this, is it just the data for Enbrel or is it comparative data, such as we were presented today?

DR. SCHWIETERMAN: Admittedly, this is a question that we don't normally ask because I completely agree with Dr. Felson. The label ought to reflect what the data show and in a way that is helpful to both the

physicians and patients alike.

Behind this question is a general recognition that the ACR20 has been questioned, both in meetings and actually in print, as a clinically-relevant endpoint, and while we don't have the time to get into that here, and I don't mean for this meeting to be a discussion of that, I wanted to get the committee's general sense of what they felt about these endpoints.

I think it's been helpful today. Clearly, there's a lot of things to measure in rheumatoid arthritis, whether it's early versus late response, whether it's radiographic endpoints, whether it's quality of life, and the relationship of all those together, and to the extent that we can present the data so that physicians and patients can make choices, I think it's helpful.

I was trying to get a feel for what the committee felt about, as much as anything else, to be honest with you, future trials and how we prioritize these particular things.

DR. ABRAMSON: I think it's a very useful thing to doctors, because this is where a lot of these very excellent drugs begin to separate from less good drugs, so that a nonsteroidal will give you an ACR20 in a significant number of patients, but when you're looking for 50s and 70s, you begin to see the impact of these new drugs.

So it's sort of like sunscreens. It's sort of like SPF30/15, and I think it's a very useful way to compare drugs.

The reason I asked about should it just be one drug versus the comparative, I would like to see it, in my own view, because you're not always looking at many drugs. The drug that's been tested should have its ACR50 and 70 response and allows you to cross in your own mind to other drugs that may not have been head-to-head with those, but to get some standard of how to compare Drug A with B.

So I would favor having -- if further people have comments? No. I'm sorry. Now it's just for the committee and the agency.

All right. On B and C, anything else you want to hear from us?

DR. SCHWIETERMAN: No. That's fine. Thank you.

DR. ABRAMSON: On D, actually we were asked to vote on D, which I guess was one of the specific requests for the day in terms of label change.

"Do these data combined with the safety experience support expanding the current indication for Enbrel to include a signs and symptoms claim for patients with early RA who have not yet received a DMARD?"

Dr. Simon?

DR. SIMON: Well, I think this question really is an extension of what Ms. Malone just asked, and I think that in thinking about it some more, what would I do as a clinician in that with the data we've now accrued, it does appear that with the speed of onset of response, that given the safety profile of comparative between methotrexate and Enbrel, that Enbrel's probably more tolerable, and under those circumstances, with at least as good a response, perhaps faster onset, you would need more methotrexate to get the same response.

I think that it is an unreasonable issue to allow to be used without failure of a DMARD.

DR. ABRAMSON: So you would be willing to catch up, let a month of improvement, without the 15 years of safety data that we have in methotrexate and a 25-year disease, make you evaluate this question a particular way?

DR. SIMON: Well, as everyone has heard me over and over again, and I was one of the few people to vote against Enbrel's approval originally because of its issue of safety, lack of a safety database that was long-term, I do believe we are iteratively accruing more and more evidence.

I think methotrexate is also a dangerous drug, and yet everybody thinks it's the gold standard, which I think it should fall from because of its lack of safety and

its risks.

So on the context of unsafe drugs, we don't know whether or not Enbrel is or is not because we have not had enough time. Given the information that we have, this is how I see it.

DR. ABRAMSON: And we'll get the data more quickly.

Any other comments? Dr. Pucino?

DR. PUCINO: I think from what we know so far, it looks pretty good for early onset for management. So I think as it's stated that this drug probably should be allowed a chance to be used.

DR. ABRAMSON: This is not a vote now.

DR. PUCINO: Oh, okay.

DR. ABRAMSON: It's just comments. I'm sorry. Go ahead.

Dr. Felson, do you want to comment?

DR. FELSON: No.

DR. ABRAMSON: Dr. Harris?

PARTICIPANT: Would you entertain a comment from the floor on this?

DR. ABRAMSON: I think not. Well, you know, David, if you want to address the pediatric issue specifically -- your term expired on this committee.

(Laughter.)

DR. ABRAMSON: So let me just speak to the other side that Lee raised.

I have a concern that because it is so effective in the short-term, that it will become a drug of first choice in the community. I'm still concerned about some of the signals of sepsis, and it's not fair to bear the burden of tumor on this drug, but I just don't think we have enough data available.

So I still share those issues. I think there is still a need to gather more information on this drug, again remembering that this drug did not come to market with the numbers of patients studied that we see with other drugs.

When we did Arava, for example, there were thousands of patients who were treated. There were 200 people treated for a year when this drug was approved and about 5 or 600 for six months, and now we're a year or two into this process with many patients treated, but many of them for relatively short periods of time, without good capture of adverse events necessarily.

So I would still wait another year in my own view.

DR. FELSON: I didn't have the courage to say what you said. I've sort of been leaning on the fence in terms of thinking about this problem because I think

there's wonderful efficacy data here, and the safety data is genuinely reassuring, I think, despite all the concerns we all had.

But the truth is I wouldn't want to give a patient with early rheumatoid arthritis this treatment without some better data on long-term safety. I wouldn't want to sentence them to potentially having a really dangerous long-term side effect without knowing more, especially since there's nothing keeping them from ultimately getting it.

This is approved. It will be straightforward for them to get a later point, and let them go ahead and, you know, try and get treated initially with something that's got proven efficacy and where the safety issues are better appreciated than this.

I think that that remains my concern. I'm still not sure, though. I think I could be convinced either way.

DR. ABRAMSON: Yes? Dr. Harris?

DR. HARRIS: You know, listening to all of this, my own view is probably more like Lee's view.

I feel that Enbrel is being used anyway, I mean, even, you know, if we say in terms of its current use. So indeed, if there is risk that we don't know, the risk will exist and occur anyway.

You know, really what we are saying is let us do it earlier. You know, let us approve it as a first line -- not first line but as a first stage.

If there's trouble down the road, you're going to get it anyway. We've approved it, and the trouble will occur. So really, I think that, one way or another, the concerns about safety really are not important in terms of what we are considering today, and certainly if anybody employs large numbers of people, you know that if they're out of work two or three months -- admittedly, it's a long disease and so on, but that difference does make a difference in terms of people's productivity, and certainly given that the safety data looks relatively good at this time early, my view is it's reasonable to get this --

DR. ABRAMSON: Let me just ask a question. Are you satisfied with the studies that are ongoing, that will capture infections sufficiently, or should there still be a little holding back, which creates an incentive to collect more data?

Suppose, for example, the four-month study, that was all there was going to be, and it was closed out, is that an issue to talk about? Once this is out, what's the incentive to -- Dr. Simon?

DR. SIMON: I recognize that we're always tending towards public policy whenever we sit and discuss

these particular questions, but in fact, that kind of answer will come out rather rapidly as we have seen over and over again as drugs get pulled from the market based on observational experience.

I really am troubled by our professional group, our rheumatology group's weddedness to the idea that methotrexate's a wonderful drug. I have found personally, as a clinician and looking at a lot of data sets over time and watching presentations here, that I don't believe it's as wonderful a drug for my patients as some other possibilities.

Having the opportunity to have such an agent as this I think is very important. Because of the lack of -- which is really represented by the health assessment quality of life issues, the fact that whenever anyone goes against methotrexate, most of the newer drugs look much better because there isn't the nausea, there isn't the other problems that methotrexate conveys even early on in therapy.

So therefore, yes, there are some significant lack of information. I'm very concerned about the long-term follow-up. I'm very concerned about the idea of understanding sepsis.

I would hope that they would study this in winter, not in summer, for only a four-month period of

time, if they're trying to answer a question of infection, when we all know when we admit our patients, hospitals are empty in the summer. They're full in the winter with people who are infected. So yes, I'm still very concerned about that.

DR. ABRAMSON: Dr. Paulus?

DR. PAULUS: I think we're discussing the question of whether we should force people to take drugs that we know are not safe before we allow them to take something that may or may not be unsafe, which we know is effective for the reasons that Lee has eloquently stated, and it's preferable to a lot of people.

The idea that this is already available on the market, therefore if a physician or patient wants to take it first, they can go ahead and take it might be true if it weren't for the control that reimbursement companies have.

So that if we say that you have to take methotrexate first, you're going to be darn hard to get anybody able to take it before methotrexate. So I think that what we're talking about is whether we as physicians and patients should have the option to make a decision which isn't going to be impeded by some bureaucracy.

The other issue that I'd like to bring up is the question of pregnancy or somebody who wants to get pregnant. We don't know whether Enbrel is safe for

somebody who wants to get pregnant, but we do know that methotrexate is not, and that leflunomide is not, and some of the other things that we use regularly and routinely are not.

So if you had a patient who wanted to start a family, who had recent onset of rheumatoid arthritis, it's conceivable that you might consider this to be your first choice drug.

DR. ABRAMSON: Okay. Dr. Brandt?

DR. BRANDT: The safety data that we heard presented are reassuring with all of the limitations that we discussed, I think, adequately, and we're not going to get long-term data soon. Long-term data are long term. They take a long time.

(Laughter.)

DR. BRANDT: I think that we've heard the advantages articulated to making this available as an option early on, and the issue of putting reins on it, if we do that, we're not going to be able to free up those reins up very soon.

If there are adverse effects that become apparent with the monitoring that's proposed, they will become apparent as they emerge in less than five years perhaps, and then we have to deal with those at that time, but I think that there are advantages with regard to

efficacy, and as far as we can see at this point, safety issues are in fact more reassuring to me than they were a year or year and a half ago.

DR. ABRAMSON: Yes?

PARTICIPANT: The point about choosing between methotrexate as the first drug versus Enbrel, I think, goes back to how much we know about methotrexate, and the fact that we feel confident about it.

I think we feel confident about using a drug that has a potential for producing significant side effects. The only thing we have is the experience to manage those complications, but actually if you talk to patients, they actually come with a list of potential things that they don't want to have when you start them on methotrexate.

So really and truly, we're dealing with that. There's the uncertainty what's going to happen in the long term, and like Dr. Brandt very clearly said, we don't know, and we will not know because it's a long-term effect.

So we are asking for the option, I think.

DR. ABRAMSON: Okay. That's a good point.

All right. I think we're probably ready to vote on this D, unless someone has a final pressing comment.

So we'll ask for a show of hands. "Do these

data support expanding the current indication for Enbrel to include signs and symptoms with early RA who have not yet received a DMARD?"

So who would answer yes to that? Just a show of hands.

(Show of hands.)

DR. ABRAMSON: And no? I'm sorry. No is -- okay.

(Show of hands.)

DR. ABRAMSON: All right. So the answer is yes.

MS. REEDY: Seven, two.

DR. ABRAMSON: Seven, two. Thank you.

Yes, sir?

DR. SIMON: Just to see if I can just sway you one more time, if the --

DR. ABRAMSON: I was already swayed. I didn't want to be like a wimp and be inconsistent.

DR. SIMON: If the original presentation a year and a half ago had included the data that we now have that they achieve ICH guidelines, I think we would have had a much more difficult time restricting the utility of this agent to only DMARD-failure patients.

DR. ABRAMSON: I would agree. The numbers last year were of great concern.

I guess the only comment, again, this shouldn't be a vote to say, you know, let the academics kind of figure out next who's, you know, and then let's -- I think we still need this issue of registry. Everything that we talked about that's being done has to be really tightened up and be more of a policy because I don't think there should be a sense that people said there's not concerns. I think it's just a --

DR. JAY SIEGEL: I want to clear up one point and also get some clarification from the committee on another before we move on. I hope I'll do this fast.

First of all, the numbers you saw at the time of approval did meet ICH standards. Now, ICH standards take into account that they may not be right for all diseases, and I won't argue that they were adequate, but we should be clear on that point.

The numbers of patients exposed and exposed for six months and 12 months were standards, and in fact, getting those numbers did in fact delay the application for several months, delayed the availability of this drug for several months, and getting larger numbers would have delayed that further, which isn't to say it shouldn't be done, but it is to say that, you know, this is the sort of trade-off that we face with drugs always.

The clarification I'd like is on 1-B, which is

what study should be done, because although you've mentioned leverage, there is, assuming we do move ahead and approve this new indication, there is still leverage. We discuss with companies commitments to do studies. We don't have a lot of leverage to make it happen, but now they publish the updates of how they're doing on those commitments on a web site, and obviously the community can exert a certain amount of leverage, and this company has done a good job as far as we know in conducting all the studies that they've committed to do.

You've mentioned a couple of times the concern about the four-month randomized study. Now, we understand, of course, long-term follow-up in a cohort study, but what we've heard from Immunex and what we're inclined to believe is that asking people who are eligible for this drug to be on placebo for periods extending four months would severely impact the ability to recruit.

So if you can design an ideal study with longer periods and then not be able to recruit into it, are you suggesting maybe that that isn't right, that it should be possible to do longer -- because the other way to get power is larger numbers. Then you don't see long-term effects, and you've made the issue that long-term effects are an issue in malignancy, but malignancy has many years of latency to present. Infections don't, and maybe large

numbers of four months is more realistic than trying to get a longer period of randomization.

DR. ABRAMSON: Well, that may be the answer. The point that we were addressing before is are there enough spontaneous infections over four months in this number of people to see that their outcome was worse, and as in the sepsis study that you referred to, it wasn't that the drug necessarily was causing sepsis, but in the context of sepsis, do you do less well, and so it's an analysis of how this study is powered for the background incidence of infections that you're likely to see, and what happens if you're on the drug?

DR. FELSON: Just to respond to a tangential issue raised by Dr. Siegel and relevant to this trial and how it was designed, I think the perception, and I think the reality is that it is very hard and probably not very ethical to recruit a lot of patients to placebo-controlled trials in rheumatoid arthritis at this point, and I think the design of the current trial and even the ultimate equivalence design of the radiologic outcome was really thoughtful and forward-thinking.

I think if I could suggest to the FDA that they ought to adopt that model, I mean, I think this is a disease that -- it's no longer really acceptable to mount large placebo-controlled trials in which placebo-assigned

patients receive no DMARD. I mean, that's just not reasonable, and you won't be able to recruit patients into a trial like that because physicians won't put their patients on those.

DR. JAY SIEGEL: Obviously, you're talking about trials such as this for a year. Are you also suggesting that four months is --

DR. FELSON: Well, I think four months is sort of the outer limit at which you could allow people, because after that time you begin to see irreversible radiographic change in placebo -- I mean, it's not really ethical to keep people on placebo, especially if they're in early progressive RA-type stage, and I think this is a real genuine concern, and I think the rheumatology community is not going to be willing to recruit patients like this into these kind of trials anyway.

DR. ABRAMSON: Dr. Garrison?

DR. GARRISON: I just wanted to reassure the committee that we have been working very closely with FDA on these issues, and we've used the best available data, which comes from some randomized trials that you've seen recently, as well as from the ARAMIS database, to try to come up with assumptions on what kind of serious infection rate we're going to see in this trial.

But we are also going to be looking at the

infection rates. We're going to have a DSMB. People are going to be evaluating these patients very carefully, and if we find that the infection rate is not where we're assuming, we will make adjustments to the trial, so that it will be a meaningful study.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: Just as an extension to what David just mentioned, the problem with the four-month data set, it's based on the idea that imaging as we know it today by x-ray, that the changes aren't necessarily so obvious in that first four-month period.

The problem, of course, is when you begin to image with MRI and other newer technologies, you begin to see damage much, much earlier, and you begin to measure much greater amounts of damage, if in fact that's what we're measuring.

So I'm only urging you to recognize that as in other things that have been iterative, this is also going to be an iterative event, and therefore whatever we decide today may be totally different tomorrow. So perhaps maybe four months is okay, but I actually doubt that.

Now, there have been multiple published reports now of even six weeks of disease having dramatic changes by MRI. If those are and turn out to be true erosions, and they are adjudicated as such, then that would suggest that

even any time on placebo is entirely unacceptable, if that's real.

DR. ABRAMSON: Okay. Janet, and then Kent.

DR. ELASHOFF: I'm just wondering why this four-month trial, which seems to be basically looking at infections, has to be placebo-controlled versus some other control, because if the infections are the issue, why do you need the placebo control versus another control?

DR. JAY SIEGEL: I think the background rate of infections in this population exists and it would be very hard to precisely determine. I don't think we could generate meaningful data otherwise.

DR. ABRAMSON: Kent? This will be the final comment for this.

DR. JOHNSON: A quick comment from Drugs.

I must say in some sense, I agree with the comment about taking an equivalence, making it from an efficacy point of view an equivalence design and having it be a safety trial. We're doing that with some big ulcer trials that have efficacy equivalence and also endpoints.

The other thing about using placebo period obviously is problematic, and the presumption is you've got background therapy, and DMARDs are going to be a part of that background therapy, and there's already a whole lot of trials that have been done with background methotrexate,

including one by this sponsor.

And the third thing is you can imbalance your randomization, and you can imbalance your time on drug, and you may just need a few months of placebo to validate your assay in essence which is what you want if you had the two other arms that are going after an equivalence comparison.

DR. JAY SIEGEL: So you were suggesting not an external control, which I responded to, but potentially like a methotrexate control or another active control or something?

DR. ELASHOFF: Like this trial we felt shed some light on whether infections were increased or not, and it didn't have a totally placebo control.

DR. ABRAMSON: Okay.

DR. SCHWIETERMAN: Just one point.

The study is not designed to deny patients standard of care. It's to deny patients the add-on of additional therapies to what they have been taking already. So many of the patients can be on methotrexate, for example, in this study, and they will be randomized to placebo.

An important point any time we discuss placebo-controlled trials, since clearly the issue is less placebo than what's being denied as standard of care and safe and efficacious therapy.

DR. ABRAMSON: So this study just needs to be examined for power and Type II error.

In terms of that, are you comfortable with where we are in this?

DR. SCHWIETERMAN: Yes, we are.

DR. ABRAMSON: I think I should just comment that this is a big issue, and I think that what we're seeing is really an outstanding collaboration between the corporation and the agency to try and grapple with a, you know, major problem, and I think everyone's doing as responsible, you know, as a model really.

I think the committee just wanted some perfection, but it sounds like you're -- some of us.

DR. SCHWIETERMAN: Thank you. The committee's advice has been very helpful here, and as time goes on, I think these questions are not going to go away but actually get more complex as there are more agents on the market.

So I appreciate the advice.

DR. ABRAMSON: Yes. Okay. So now, to the question in Number 3, "Radiographic measures. The design of this trial was changed from one to establish the superiority of Enbrel over methotrexate to one to establish non-inferiority of the equivalence of Enbrel to methotrexate with regard to radiographic outcomes. However, the absence of an adequate historical trial

database establishing the degree of efficacy of methotrexate on radiographic changes in early RA precludes drawing definitive conclusions from the latter analyses."

So "Please discuss whether there is a basis for concluding that the methotrexate effect in the population studied is large enough that the non-inferiority data suggest that Enbrel also has an effect which surpasses that of placebo."

DR. JAY SIEGEL: Let me put that in plain language.

We could argue probably forever as to whether the methotrexate effect is four units and whether we should exclude 70 or 80 percent or whatever, but nuts and bolts, coming down to brass tacks or whatever the right metaphor is, if you compare the two, the outer limit of the confidence interval is .3 or .2. I think .29 and .16 were the numbers we saw. I don't like excessive precision in these measures, but depending on whether you use a 90 or 95 percent confidence interval, what this question really boils down to is, if you assume -- you know, the natural progression of the disease here is four or six units, and we don't have a direct -- four to six units, depending on which data you look at early on of total Sharp score per year.

We don't have a direct data of methotrexate

effect early on. We have it later on, but if you assume that it has an effect of at least .3 units, then you can draw from this comparison that Enbrel, which had a point estimate that was .5 better, and at worse, .3 worse, also has some effect, and so that's sort of what the question is getting at, is that.

Although not firmly data-driven, rather than looking at whether we believe it has an effect of four units or not, is it reasonable to presume, based on what we know about the disease and about methotrexate, that its effect is at least that large, in which case this provides some evidence of activity and efficacy?

DR. ABRAMSON: Dr. Mills, would you like to address this question first?

DR. MILLS: Well, from the standpoint of several things. One, that you have to look at in terms of the historical data that has been provided for us from over the years of literature, we don't have a nice trial with methotrexate in this population to be able to address and say that indeed it's four to six, and we have a high confidence.

So from the standpoint here, you have to be somewhat reluctant to take a big step forward in this area.

From the standpoint Immunex has provided us an outstanding look at this group over one year, but this is a

disease process that's going over many years, and so when looking at this, in looking at the historical data, and we're very reluctant to take Step 4 and say obviously this four to six window is going to be an idealized known given for us, and so that we can take this data and extend it, that's what we're looking for in terms of the input from the group here, is to give us some idea as to where we should take this data, and what we should look at long-term, because my concern is one year versus a long-term disease process.

DR. ABRAMSON: But this gets a bit to the placebo discussion we were having. It's real hard to put a one- or two-year placebo arm into a radiographic study these days.

So I guess you're kind of looking at equivalence or comparability to your comparator drugs arguably, but I don't know.

Janet, do you want to respond?

DR. ELASHOFF: Well, strictly speaking, taking only the non-inferiority comparison by itself, I don't think you can conclude that Enbrel has an effect superior to placebo.

This is a different group than those historical controls have been based on, and to some extent, almost never in a trial without placebo can you be really sure

that you're having an active effect.

I certainly understand why we don't want to use placebo, and it's a good idea to try not to, but you're always in the position, I think, of not being entirely sure that it works.

In this case, you have other measurements that do look better, so that supports the non-inferiority claim, but I think you always have a doubt in any trial like this.

DR. ABRAMSON: So if they showed equivalency to methotrexate, how could you design a study except by comparison to another drug?

Janet, I'm wondering in terms of that dilemma.

DR. JAY SIEGEL: Let me address that.

I'm actually quite involved in policy development internationally in this area and other areas, and I think her comments are right on target.

In some sense, you can never be certain about showing efficacy from non-inferiority trials because the margin that you set is based on a historical analysis of prior trials of the active control, and whenever you're comparing across trials, there's so many questions about the design and conduct, nature of patients, concomitant therapy, that all the concerns that arise with any historically-controlled trial arise in those underlying assumptions and the applicability of them.

So the bigger question is what can you do? Well, we're at a setting, at least in the long-term probably, where placebo-controlled trials cannot be done. This happens in a lot of diseases. That leaves you with active control trials.

You cannot make an active control non-inferiority comparison valid simply because you have no other option. If it's not scientifically valid, if there's no way to say, well, I know methotrexate has an effect at least this large, then there's no way to say for sure that you can show by non-inferiority an effect.

What we have here as the comments, I think, correctly describe, though, is something -- so first, in the theoretical where are you left, well, you're left is that this is an area in which you should design a superiority trial. That's what was done, and that's what should have, I think, remained.

Now, here we have an ironic situation, where the superiority trial was done and had its data as a superiority trial. It would have won on its preselected primary endpoint which was erosions. It was changed to a non-inferiority trial because there were data on methotrexate effect on Sharp score and not on erosions alone.

It was changed, I should say, for a good

reason, which was that there were inquiries that are appropriate about, well, would a non-inferiority finding be used as evidence of efficacy, and because if you think it should be, then it's best to consider how you would handle that prospectively, and the company put forward margins and percent retained numbers that they felt were appropriate ones to use prospectively, and if you're going to make that case, it's much better to do that prospectively.

But what we have is, you know, we're asking about this in B, then is that the effect on erosions, some of the effects at six months, a number of effects which would suggest superiority, which, unless you assume that methotrexate is harmful, which there's no data to suggest in this population on those outcomes, then that provides intrinsically evidence of activity.

But what we're asking about in A is the non-inferiority design and the extent to which that provides evidence, and the reason one might presume it provides evidence is that if you accept again the historical data that the natural progression is at four units a year or at six units a year, and then -- and methotrexate in this study -- the arm progressed at 1.3 units, and the Enbrel arm at .8 units, plus or minus .7 maybe, even if the natural progression of this population had been as low as two, there is, based on historical controls, the suggestion

that it would be superior than placebo, but also, and I think importantly, based on comparison to methotrexate, there's a suggestion that it's within .3 of methotrexate, that at worse, the progression rate is .3 faster than methotrexate.

Again, as I stated in explaining Question A -- and my apologies for being overly wordy, but these are tough concepts, I think, and they're tough to face anew -- but if one can assume in this population, even though one doesn't have direct data, if one has a reasonably-strong presumption that methotrexate has an effect larger than .3, then these data, and I would agree entirely with the comment, they don't provide definitive evidence.

In fact, our question precludes drawing definitive conclusions, but that's part of the picture of what may or may not be a compelling picture taken in toto.

DR. ABRAMSON: Dr. Simon?

DR. SIMON: It seems like this is the classic conundrum, and perhaps you could help me understand it in the context of the regulatory guidance document, that clearly all of this brouhaha is created because it's not adhering to the guidance document, I presume, in that the world accepts methotrexate as a DMARD.

They throw that term around all the time. It's never been adjudicated that way. It's not been registered

this way by the FDA. It's not labeled as such, as altering structure by the FDA, that I'm aware of, and I also understand that the guidance document that was just out in 1999, I think, not so long ago, I presume the issue is to gain a label, such as altering structure, that you have to demonstrate that you're better than placebo in doing that, is that correct?

DR. SCHWIETERMAN: I'd have to go back to the guidance document and check the exact language. Certainly the spirit of it wasn't necessarily that all trials would need to be placebo-controlled trials for a 12-month study, but I don't have the guidance document in front of me to actually refer exactly to what you're --

DR. ABRAMSON: Dr. Johnson might be more ready to answer that.

DR. JOHNSON: I pretty much have it in my brain, I'm afraid. Well, we fudged the issue is what it amounted to, and we said that it's preferable.

We probably made some allusion to the fact that if there are no established active controls, then you need to do a negatively-controlled trial, which doesn't necessarily mean placebo could be a lower dose.

But we also said something about in assembling the evidence, it is desirable that at least one trial be a difference trial or something to that effect. Now, we

didn't say specifically which claim that was directed toward, and the other thing that's been brought up, but I don't think been emphasized enough, is that we, too, are uncomfortable with an x-ray claim, period, which is why we wanted it hinged to a clinical claim. It wasn't a freestanding claim like the others, unless it was a dramatic x-ray effect, which we also couldn't describe, though it attempted to in terms of the erosions. That question was asked earlier.

DR. ABRAMSON: Dr. Sharp?

DR. SHARP: I'm a little uncomfortable with all the discussion about six points or four points or two points, because when you look at different people who are reading films and scoring them, nobody scores exactly the same.

I think the more critical issue here is how reliable is the methotrexate effect. Now, that can be expressed as a percent, and you don't have to have absolute figures, although the model that FDA required Immunex to create, they had to plug in some figures.

I think you can do the whole thing without specific figures, and you could even take the figures that are already available from the study and say if methotrexate had 50 percent effect or 60 percent effect or 40 percent effect, you could look at it that way, and my

guess is that that circumvent a lot of the discussion here about so many points, and I don't think it would come up with any different answer than they have gotten so far.

There was one other point, but I guess it slipped my mind.

DR. ABRAMSON: You can come back.

DR. JAY SIEGEL: Let me just say that there's nothing in this sort of design or model that would preclude doing it that way, absolutely, but we still don't have the data in this early population as to what percent effect methotrexate has.

DR. SHARP: Oh, that was the point I was going to make.

In terms of the effectiveness early versus late, I must say I'm intrigued with the data in this particular trial that makes it look like methotrexate was much more effective in treating early RA than it was later on.

However, in the Arava trial, the leflunomide, 40 percent of those patients on methotrexate were less than two years' duration. Now, there's still a discrepancy between the two populations, but I think that's reassuring, and in that particular trial, there was no difference in the effectiveness of methotrexate early or late.

DR. ABRAMSON: Thank you.

I think I need a clarification as to what we're trying to address here, because there's statistical issues of definitions of non-inferiority and superiority in this. But then there's the issue of whether a historical control is valid in this setting, and I think they're two distinct issues.

So I guess the question is if it were true that methotrexate and Enbrel were equivalent in their effect, if we assume that for the moment, what question do we need to address in terms of the ability to make a statement about concluding that therefore Enbrel protects against radiographic progression?

Let's assume for the moment that there's not a statistical question and take for granted or presume that these two drugs have equivalent effects from your perspective.

DR. JAY SIEGEL: If you assume they have equivalent effects, all you need to know additionally is that methotrexate has an effect, but obviously we don't know that they have equivalent effects. We know a confidence interval around the effects.

So really, what we need to get at to answer this question, to put it in a non-statistical but a scientific term, is we need to know how much effect it's reasonable to presume that methotrexate has in this

population under these conditions.

To put it simply, if two drugs had exactly the same effect, but you studied them in a refractory population or in a population in which neither worked, then you might well get up with a lot of precision that they have the same effect, but it would not be evidence of efficacy because they could have the same lack of effect rather than the same effect.

So by showing that this is similar to methotrexate or at worse, .2 or .3 worse than methotrexate, one can only conclude that that means there's efficacy if we can conclude that methotrexate has an effect in this population, and obviously there's not direct data. So it may not be a conclusive determination, but what we need to know, what we need to hear, and I think what you need to think about, is does being within .3 units in Sharp score progression of methotrexate provide evidence of efficacy on the basis of a presumption, if not proof, that methotrexate surely has at least that much benefit?

DR. ABRAMSON: Right. So let me still sort out these two issues for a moment, though.

We have two studies that I'm aware of that methotrexate is effective. One is the Rich paper, which I've not read, and the other is the Arava data, in which Arava and methotrexate both did well. So the question is,

is there sufficient evidence that methotrexate is better than placebo is a first question?

Lee?

DR. SIMON: Well, that's really the problem, because there is sufficient evidence that methotrexate's better than placebo based on the Arava data set.

However, that patient population was different than this patient population. However, if you'll just bear with me in a Talmudic way, if you believe that the patients had more disease, meaning longer-term disease, in the Arava data set, even with 40 percent with less than two years of disease, where this population was all less than three years of disease, you had a similar kind of biologic measurable signs and symptoms response which was reasonably correlatable to the predictable x-ray response in the Arava data set. That also has happened here.

So why should someone expect that a drug that worked in an older population would not work in a younger population -- meaning, you know, not as long disease -- that gave you a similar signs and symptoms response? Meaning why should that be disparate? Why should that be separated? We're already making so many assumptions, that it's not unreasonable to make that great leap in this circumstance with this lack of information.

The dilemma that I have is that inherent to

this data set, which is I think is fascinating, is a biologic discrepancy. There is a big difference between joint-space narrowing effects and erosion effects, and it seems to be even bigger when you've had more disease for longer periods of time.

What we know biologically of how erosions take place, meaning osteo class-driven, cytokine-driven events, that may be a very different phenomenon from joint-space narrowing. The dissolution of cartilage may progress at a very different rate and respond to different things.

Nonetheless, I do think that we can argue this forever, but if we're going to accept the Arava data set, we have to accept the reality that there is similar responses between Enbrel and methotrexate in inherent decrease in progression, and it seems real.

DR. ABRAMSON: So you think there is evidence that methotrexate retards x-ray progression, based on the available data?

DR. SIMON: I would say that, based on the available data, it appears that methotrexate does slow progression of disease.

DR. JAY SIEGEL: And if I understand your logic, let me get this clarification, you're saying, in addition to that, that while there isn't evidence in early disease, it's not an unreasonable presumption that it would

be as effective or more effective in early disease than in later disease?

DR. SIMON: Given the fact that 40 percent of the population in the Arava data set did have early disease, that there weren't discrepant behaviors in that patient population, I think that's a reasonable assumption.

DR. ABRAMSON: Immunex, please.

DR. VAN DER HEIJDE: I would like to add to that, that it's all circumstantial evidence that we have, that if you look to the data that is available at this moment, it looks that there seems to be a linear rate in progression. So that's the progression that can be seen later on in disease is also seen in early disease, and studies that are against that, they show that there is more progression in early disease, not less progression in early disease.

So then I think the minimum, if you want to have a number, would be four, and in early disease, it would even be higher and not lower.

If you take the study that was mentioned by David Felson, is that if you have methotrexate as an early drug, it's more effective than using it later on. This would make it seem unlogical that it would not work in early disease, and in all the trials I've seen that x-rays were involved, it's very rare that in an early disease

population, it's such a low rate of progression as around one.

DR. ABRAMSON: Dr. Felson?

DR. FELSON: Yes, there is actually another -- it's a meta-analysis of comparative trials with methotrexate in second-line drugs, and actually the first author is Graciela Alarcon, who's here, who was in the Journal of Rheumatology, and it shows I thought very nicely that methotrexate, compared to other second-line drugs which have approval for structural modification, is as or more effective than those drugs in preventing. So that's indirect evidence of methotrexate's effect on inhibiting structural progression.

I don't know if Graciela wants to comment on her own study.

DR. SHARP: She probably does.

(Laughter.)

DR. SHARP: We're talking about, was it, two studies you came up with? There are additional studies, besides that. Jurisin compared methotrexate to Imuran, and there's no reason to believe that Imuran is worse than placebo, and methotrexate was significantly better, and Weinblatt and Barbara Wiseman at Boston compared methotrexate to auranofin, and it was better. Again, I don't think auranofin is worse than placebo.

DR. ALARCON: Actually, I didn't want to bring the meta-analysis because that actually is a collection of data from the 1980s with patients with longstanding disease, and I didn't think it was fair to compare it to the patients.

The Rich study, though, I believe, is our study as well, and this is a study which is small and dirty, done by a fellow in -- that doesn't mean all the fellows are dirty workers, but the point is that it was no money, just he wanted to look at what happened when you administer methotrexate as the first DMARD.

So given all those limitations, what we show is the patients that didn't have erosions to begin with, the probability that you don't develop erosions is much greater than if you already have erosions to begin with using methotrexate as the first DMARD.

DR. ABRAMSON: Thank you.

So I guess for the piece of this, the consensus that we have is that methotrexate, given studies that are imperfect, the literature that exists supports methotrexate as effective in retarding progression, I think, the way the literature is there.

So now the question is the second half of this question. Is the study valid from a statistical point of view?

Janet, I don't know if you were going to comment on that or you want to make another comment.

DR. ELASHOFF: It was another comment.

The extent to which we start relying on historical control to flesh out the conclusion means that it's more important to be collecting a lot of potential predictor information and analyzing that in as much detail as possible because that is relevant to these issues of how much early versus late and this kind of patient versus that kind of patient, and is this population really applicable to that, and presumably one could in fact do something in this other study that people are quoting to compare the early versus the late in that data.

DR. ABRAMSON: So now, the other piece of this question, I think, is only selected people can really debate effectively, and that's this issue of superiority and non-inferiority.

I'd ask the people who understand that issue, I don't know, Janet or David, to make some comments on it.

DR. ELASHOFF: Okay. I don't think much of the definition of non-inferiority that was used here.

However, the actual confidence interval is suggestive that they're pretty close, and as other people said, the other evidence, which is presumably relatively correlated with this, erosion specifically did come out

superior.

So in this particular trial, I'm not especially worried about that issue, but in other trials, one could be extremely worried about the non-inferiority serving as a basis for a claim.

DR. JAY SIEGEL: Thank you. I think that's useful.

I would point out that if this trial had not been changed to non-inferiority but used the same endpoints that it's using as a non-inferiority trial, we'd be having much the same discussion because what we would be looking at would be a very near-miss on this primary endpoint of total Sharp score and some important data on the erosions and other endpoints which suggest activity and a near-miss, but not against placebo, a near-miss against a drug that we all believe to have some activity, and so in a sense, for those who haven't quite caught on to all the non-inferiority concepts, you could look at it that way.

Does a near-miss to being superior to an active control on one endpoint with support of secondary endpoints in which there was suggestion of superiority add up to evidence of efficacy?

DR. ABRAMSON: I think we've been discussing B. Let me read it.

"To what extent do other radiographic

endpoints, including data on the number of erosions at six and 12 months original primary endpoint, and data on the six-month Sharp score support the efficacy of Enbrel in delaying radiographic progression?"

So I guess, Dr. Siegel, has this been addressed in these -- Ken?

DR. BRANDT: Yes. I'd like to ask a question for clarification or for edification, and I guess to Dr. Sharp, and it relates to the issue of the total Sharp score and the contribution thereto of narrowing as opposed to erosions.

Certainly if we look at knees and standard radiography, there are all sorts of terrible issues that relate to joint-space narrowing that pertain to positioning and reproducibility of positioning, especially in a multicenter study, where radiographs were obtained in multiple cities.

Can we be confident that narrowing as you see it on the film is true narrowing and not related to position? Have there ever been correlations made between, say, cartilage thickness by MRI and joint-space measurements on a radiograph in rheumatoid hands?

Do we know that we're really looking at cartilage thinning? Lee brought this issue up a few minutes ago.

DR. SHARP: Well, I don't know that we can establish it's always cartilage thinning.

I think the book of the evidence is that it usually is. In a very lax joint, you can have distraction, of course, and a lax joint again with an excess amount of fluid, you might have spurious widening, if you will.

I did some simple geometric calculations of how much impact a change in focal distance, for example, x-ray tube to hand, would make in joint space, and it's obviously quite significant in hips and knees, but it's a few hundredths of a millimeter in finger and wrist for reasonable assumptions. So I don't think that's very likely to be an issue in terms of joint-space narrowing.

The whole question -- if you want me to address it now -- the whole question of joint-space narrowing and erosion, I think, is a very interesting one. Is it appropriate?

DR. ABRAMSON: Yes, please.

DR. SHARP: Together with my colleagues back in Houston back in the 1960s, we started developing a method for scoring the radiographs. We were convinced that erosion and narrowing were separate phenomena, and everything that's happened since then has tended to convince me that we were correct in doing so, particularly what Lee referred to a minute ago.

The pathogenetic mechanisms now are, I think, reasonably well worked out. I think it's fairly conclusive that osteo class driven by TNF-alpha and IL1-beta and perhaps activated T cells produce a factor that helps to generate osteo class. There's a recent paper from Lee's institution in the ANR about that. That is related to the development of erosions.

I don't know that there's very much proof, but I think most of us believe that metalaproteases are responsible for loss of cartilage. Maybe Ken Brandt wants to comment on that.

With these two different mechanisms, I think it's not at all surprising that we come up with a different result for erosion and joint-space narrowing.

Put it up, yes.

Historically, in many studies, joint-space narrowing has been as important or more important in discriminating between two different kinds of treatment, and as a matter of fact, in the Arava study that's been referred to so often, the P value for joint-space narrowing comparing methotrexate to placebo was a good deal lower than for erosions.

Now, here, the joint-space narrowing score comparing Enbrel to methotrexate are about the same. One would therefore conclude that you're having an effect on

narrowing by Enbrel, and erosion scores are different in that Enbrel appears to be having more effect than methotrexate, and I think that merely tells us that Enbrel works better in terms of some of the things that drive erosions.

But it also works against the joint-space narrowing. It just doesn't show a difference with methotrexate.

DR. ABRAMSON: Perhaps, Dr. Sharp, you can help us with one of the next questions, which says, "Please comment on the use of erosion scores versus the Sharp score as a preferred outcome measure."

So do you lose information by combining these two endpoints?

DR. SHARP: I don't think you lose information.

Well, the Sharp total score is a composite score, narrowing and erosion, and the two are associated. There's a highly-significant, statistically-significant association, but they're not tightly linked. The two are driven separately, and I think in a large database, I've forgotten the exact figures, but I believe it's about .6 for Pearson correlation coefficient between the narrowing scores and the erosion scores.

Now, a composite score, if they're both working, you get a little bit extra lift out of it using