your composite score.

I think many rheumatologists focus on erosions because although they're not specific for rheumatoid, they're pretty close to that. They're fairly unique in rheumatoid. You don't see erosions in very many other situations, and certainly the pattern of erosions is quite specific.

DR. ABRAMSON: This losing information means the failure to pick up differences in the action of a drug, for example, as you showed between erosions and joint-space narrowing.

Dr. Brandt?

DR. BRANDT: There's another issue, and that relates to looking at this as means, as we saw in that last slide, and again, I guess it's a reflection of disease with narrowing, how often does narrowing improve in individual patients?

DR. SHARP: We've always assumed that was reader error.

(Laughter.)

DR. BRANDT: Maybe not.

DR. SHARP: Maybe not.

I think in terms of some of the swelling that may occur in cartilage in the early stages of osteoarthritis, there may well be some improvement, if you

will, but I don't know that we can rely on detecting it by current methods.

Now, I think some of the computer-based methods that actually measure joint space and some of the things that I've been interested in, perhaps we could, because it's -- you can really measure very fine differences.

That's an interesting point. Since I brought that up, in looking at an old database I have, doing actual measurements of joint space didn't behave any better in discriminating between gold therapy and placebo in scoring. Scoring is basically pretty reliable.

DR. BRANDT: Years and years ago, Dave Hammerman showed in histochemical studies of rheumatoid articular cartilage in areas very remote from pannus, depletion of proteoglycans, particularly in the middle zone, and I'm not sure that that's not reversible.

DR. ABRAMSON: We're going to have -- thank you -- one comment from Lee, and then we need to sort of move along and get through the questions.

DR. SIMON: Well, actually, I'm just a little uncomfortable with what Ken just said. You may believe that that may be reversible, but remember that a lot of the evidence that we're talking about are people with long-term disease, not short-term disease, and I'm not aware of a lot of good data after 20 years of rheumatoid arthritis where

we have evidence that Highland cartilage is repaired to the extent that you have normalized joint space under those circumstances.

You theoretically may be correct in the early on disease. I'm still a little uncomfortable making that assumption in the longer-term disease.

DR. ABRAMSON: Thank you.

Let's go back to Question B, because, ultimately, Question F, we need to take a vote on, and in many ways, B becomes a critical discussion point that we need to come back to.

So "To what extent do other radiographic endpoints, including data on the number of erosions at six and 12 months and data on the sixth-month Sharp score, support the efficacy of Enbrel in delaying radiographic progression?"

Again, I'd like to hear first from Dr. Mills as a radiologist on the panel here.

DR. MILLS: From the standpoint here, looking over all of these films, you do have evidence that the radiographic changes are being delayed through one year.

Now, from that standpoint, what is the relevance, and what's the credibility of that result for you as a panel to look at?

My concern is for you to again realize that

you've got a patient population that's early RA. You have a grouping you're evaluating, and you're saying we are seeing some radiographic delay. You don't have a long-term follow-up, and you don't have a good historical comparative data set to work with.

But, yes, the radiographic findings are there. They're very reproducible in terms of the analysis. We're able to determine them, and again we have an excellent data set from Immunex to say those findings are real. Now, the significance is what we're asking for.

DR. ABRAMSON: What do you think about the separation of Enbrel from methotrexate and the erosion score?

DR. MILLS: Do I feel that there's a width there that's adequate?

DR. ABRAMSON: Yes.

DR. MILLS: It's my impression in looking at the data that it's adequate, but that's for you to come back. You know, that is my opinion in looking over the information.

Whether or not that that means clinically -- remember, you're taking care of the patient, not the x-ray, in terms of what does that mean for you.

DR. ABRAMSON: Any other comments on Question B?

(No response.)

DR. ABRAMSON: Okay. Let's skip to Question E. "Please comment on the apparent" --

DR. JAY SIEGEL: Can I ask something about D? Because it follows on all these discussions and on the comments by Dr. Sharp and Dr. Simon.

So the pathophysiology is different, and based on that pathophysiology, you might expect an anti-TNF to have more effect on erosions, and in fact, in this trial, it appears that that may have been the case, and that is in fact what was prospectively looked at, and so my question is, if, on the next trial of Enbrel or some other anti-TNF, somebody wants to use erosions as a primary outcome for radiographic assessment as opposed to Sharp score, is there likely to be objection from this committee to doing that, if that's what they feel is the most sensitive measure for the effect of that drug?

DR. ABRAMSON: Well, I mean, I think we are --

DR. JAY SIEGEL: You're going to reserve the right to object to anything, right?

DR. ABRAMSON: I think we don't understand the pathophysiology of those two processes very well. We're just learning about it.

I think it's important to collect information so that you can make these discriminations because then you

may learn from this kind of study to go back into the biology of the differences.

So I would answer yes, that I think that these may be two separate things. They're both very important, and they should not necessarily have to have both in my own view.

DR. FELSON: Just to play devil's advocate, I guess I would say no.

I mean, I think that it sort of gets at the central question of what we're interested in when we talk about preventing structural deterioration anyway.

Are we interested in using a biomarker of a synovial pannus eroding into bone at the lateral margin of a joint or are we interested more in the sort of global impression of what's happening to the structure of the joint as it progresses in rheumatoid arthritis?

I think I would argue that the latter is what we're interested in, and the best way we know how to define that latter entity, that latter construct, is by using some kind of summary score, either a summary joint-space narrowing/erosion score or the Larsen score, which summarizes it as a global score, and which I don't think any of us are recommending using, but I think to focus on erosions alone doesn't necessarily give us what I think in the clinical trial methodology groups we would call content

validity, meaning it doesn't give us the range of outcomes we're interested in.

It doesn't get the whole picture of what goes on in the joint, which is structural deterioration.

DR. ABRAMSON: Okay. Lee?

DR. SIMON: But my problem with that, David, is that the structural deterioration may take place at a certain point, regardless of how much active inflammatory disease is taking place.

So therefore, although it's convenient and nice and may achieve a certain validity in the kinds of studies that you're talking about, it may actually reject the provision or the reality that a certain amount of damage will ensue, and that we consider the osteoarthritis of the burnt-out rheumatoid arthritis.

So thus, one might actually get a good response to the drug to stop the disease, and yet because so much damage had already taken place, there's still further progression that you would not alter with the particular intervention that you're using.

So I think that the problem is, is that we're short of understanding all the biology. We have a lousy imaging technology, although it's the best that we have. There's more stuff coming on the horizon maybe that will help us a lot more, and no one has really done a good job

of correlating the x-ray change to function.

So we don't even know what the small x-ray change means in the context of what you asked for, is what's important for the clinical outcome.

DR. ABRAMSON: Yes?

DR. MILLS: I'd like to make a comment, also, in terms of getting all of the information. You certainly want it all.

My concern right now in seeing the data from this trial is that we appear to have two different response rates that are working. Your joint-space narrowing seems to be working at a different time interval, certainly not in this interval for this patient group; whereas, the erosions are being affected.

So you want to get all of the information and certainly bring it back to the clinical evaluation. The concern is, is that we are seeing these different response rates. So they may propose a trial to us with erosions only, but we want to see all of the data to come in, so this committee can assess it, because, frankly, you have a very limited historical data set right now, which time we reach back for it, we find it is to certain extents flawed, and so when extending back into our evaluation, we say, we've got to have this data and evolve it from here.

DR. ABRAMSON: You know, it's a very important

discussion because we've taken x-rays to become a gold standard, when in fact they're the surrogate endpoint for clinical outcome.

So now we begin to get this data, and we have to then validate what's predictive of disability and problems. So it's another piece of information that's not available.

DR. FINCK: Can I just add as the sponsor that I don't think there'd be a time when we would only read for erosions.

DR. ABRAMSON: Right.

DR. FINCK: Obviously, we want as much complete data on the pathophysiology of this as the members of the committee.

But I do think there are differences in the way drugs work and how they affect the mechanisms, and that you might actually see a differential effect as we saw in this trial.

DR. ABRAMSON: Right.

DR. JAY SIEGEL: And the question was not suggesting that one should only read for one element, but one likes prospectively to determine a primary measure for various reasons.

DR. ABRAMSON: David?

DR. FELSON: I guess I want to make a

measurement comment, which is, I'm not sure you saw different effects in this trial.

I mean, you saw parallel curves for methotrexate and Enbrel for joint-space narrowing, and if one assumes that methotrexate has substantial effects on joint-space narrowing, then Enbrel does, also.

Okay. You saw slightly greater effects in erosions, and I'm not sure that the differential effects are really clinically important or meaningful. I mean, it's just not at all clear that the distinctions that are being made among all these different trials in terms of what changes with what are all that meaningful.

DR. ABRAMSON: One last comment from Dr. Sharp, and then we'll go to F.

DR. SHARP: I have a comment that x-ray changes don't correlate well with other things.

There are many studies that show that the x-ray score correlates not at a very tight level but correlates with function, correlates with deformities, correlates with limitation of motion.

We know that there are measurement problems with some of these, and we also know that the curve against time of disability is a different shape than x-ray. Disability early in the disease is pain and swelling. Later on, it's anatomical damage.

But these things do correlate, and if you project the change that we see over one year of observation over, say, a 25-year life span of many patients with rheumatoid, the difference between really active treatment and placebo in bygone years when placebo treatment was legitimate is really very striking, and you would predict there'd be a big difference in the functional ability and the deformities at the end of 25 years of effective treatment, and that assumes that treatment continues to be effective throughout, which we don't necessarily know at this point.

DR. ABRAMSON: Okay. Thank you.

All right. Let's move on to the last question on this page.

"This trial was conducted in patients with early RA, less than three years' duration. Do the data support a claim that Enbrel delays radiographic progression in patients with early RA? And to what extent can the radiographic data be generalized to patients with longstanding disease to support a general claim for delaying radiographic progression?"

So anyone like to comment first on this? Yes, Dr. Simon?

DR. SIMON: Well, I actually have a question as it relates to this question, because the slide that was

presented by the sponsor didn't use this terminology.

What are we asking in that context? Are we talking about just slowing progression or are we talking about prevention of damage?

DR. JAY SIEGEL: Well, on the slide I guess the sponsor used the word "preventing," and maybe the guidance document uses the word "preventing."

As you see from the data in this trial, progression occurred on both arms. Neither arm was better or even as well off at the end of the trial as they were at the beginning of the trial, and I don't think, if you read the document, it wasn't presumed that the standard for getting a claim regarding progression was that there be no progression whatsoever, that the disease stabilized, and that's why the question is in terms of whether there could be a claim of delaying. Maybe there's other wording that would be better than delaying, but diminishing or whatever.

DR. SIMON: Well, that reason that becomes even more important is they did show other slides that showed evidence there were no new erosions, and I became confused because that could be construed as not having new erosions as a more biologically-evident event that you've prevented that disease process, because the progression of erosions may not be due to ongoing inflammatory disease. It may be due to the previous damage that took place that couldn't be

healed, and so I think this is a much more complex issue, and I think it does turn on what data we have, which is, what emphasis would we place on the data showing no new erosions in this year-long period, and were there any differences between the two products in that context?

We've not had good evidence before about no new erosions in the historical data sets that we've already referred to. So I think that there is something that we have to grapple with there, and then the other issue is, is that it probably did slow progression, but how important that is, I don't understand.

DR. ABRAMSON: All right. To add to that, we based a lot of our prior discussion on using the historical controls in the literature, and we referred to the leflunomide database, and leflunomide does have approval, have some language in the label about preventing progression.

At some level, we have to discuss how comparable this language needs to be, since we base some of our conclusions on the comparator methotrexate in that study.

So to the extent that this says more than that label says, I think we have to be careful, and I think we need to discuss that.

Kent?

DR. JOHNSON: I think, actually, if that was the language we used, it may have been a mistake, because it speaks to a higher achievement than actually usually occurs, and we've actually remedied that in the OA document that's rolling along.

It should be pointed out, and maybe everybody's aware of this, that we have not recognized -- in the document, anyway -- a stand-alone claim, as I mentioned before, and leflunomide was approved on the basis of a couple trials, both of which had a placebo anchor, and from an evidentiary point of view, the methotrexate was irrelevant and the sulfasalazine which were the active controls.

DR. ABRAMSON: Okay. All right. So any other comments on this?

(No response.)

DR. ABRAMSON: Can you give us a clarification then in terms of Lee's comment and the Arava, as to, if we are going to take a vote here --

DR. SIMON: What are we voting on?

DR. ABRAMSON: Yes. What are we voting on? Are we in essence endorsing the request for the label change or are we -- you know, what is it then?

DR. JAY SIEGEL: Well, we need advice as to what to label, if anything, regarding the x-rays.

I guess I would say that I think that's potentially an important point. Jeff may be able to address it or the company better than I can, the difference between progression that occurs from expansion of preexisting lesions versus the development of new lesions.

I would let it suffice from my remarks to say that that's an exploratory analysis, that the measurement of erosion as primary analysis was the measurement as done in the Sharp score, which takes into account both of those, and it is with regard to that measurement that I was commenting that both groups progressed, although arguably greater progression on methotrexate.

Although I wouldn't want to restrict your thinking to the wording that we put here, I think that Kent's comments would be consistent with mine, that given this sort of finding, if we believe it merits a claim that the right wording isn't to prevent progression, if in fact there's less progression on one arm than the other arm, and whether the right wording is "delays progression" or some other is something we'd be open to, but I think the bigger question is, is there enough meaningful data about the effects of progression to indicate that this does affect x-ray progression, and then we can figure from there what sort of wording.

The second part of the question, of course,

relates to our concern if we know it happens in a one-year database, in fact, and the biggest difference was at six months, and obviously simply because the trial only lasted a year, we don't know beyond that, does that support a general claim or a claim for the first year of treatment or what?

DR. ABRAMSON: Bill?

DR. SCHWIETERMAN: Yes. I'd just like to second what Jay had to say.

The issues about radiographic progression, unfortunately, make the guidance document obsolete because there's no discussion about many of these issues. Healing of erosions, patients who are non-progressing, delaying radiographic progression and so forth. There's no hierarchy of claims in that particular subset, all of which matter.

We're not sure what those answers mean, but we deliberately did not phrase questions in this particular meeting here because there was enough on the agenda already, and, B, it would be, I think, a little bit premature to go into this at this particular point but not really premature.

Suffice it to say that this committee will be seeing from the agency questions and potential changes to the guidance document and all these things because we're

having to face these questions right now, the sponsors that are coming to us.

DR. ABRAMSON: Okay. So why doesn't the committee look at the first question under F?

"Do the data support a claim that Enbrel delays radiographic progression in patients with early RA?"

Before we take a vote on this, are there any other comments that people want to make? Janet?

DR. ELASHOFF: It seems to me that the claim, the more specific one is about what the data show, the more defensible the claim. So what we specifically, for example, see is a lower erosion score rather than more general words, like radiographic, more general words, like progression, and more general words, like delay.

DR. ABRAMSON: Well, you see some comparability to methotrexate, which, as we said before, might be preventing joint-space narrowing by previous studies.

DR. SIMON: In the comment you made before, are we not trying to set a new bar here?

I mean, the problem is, is that we do have precedent, and I would like to know what was written in the Arava label, because that really does make a difference, because whatever that said, we have to be careful to construct this in a similar fashion, if we believe this evidence is real.

So could somebody help me with this?

DR. ABRAMSON: Where's the PDR?

DR. GARRISON: We have the Arava label, if you would like it.

DR. ABRAMSON: Okay. Perfect. Thank you.

DR. SIMON: That's exactly what I was going to suggest, that in fact as per Janet's observation, this is addressing the observations. We can choose to maximize and minimize based on the issue, but it addresses all the questions we've really asked just now.

DR. ABRAMSON: All right. So the caveat in the first question here, though, is the phrase "early disease," because I guess that -- so, let's take a vote just on that.

Assuming that the "delays radiographic progression" for the moment includes language on retardation, let's have a show of hands for those who believe that Enbrel delays radiographic progression in patients with early RA.

(Show of hands.)

DR. ABRAMSON: Okay. So it's --

MS. REEDY: Unanimous.

DR. ABRAMSON: So the harder question, "To what extent can the radiographic data be generalized to patients with longstanding disease to support a general claim for delaying radiographic progression?"

Again, given that the Arava thing is non-qualifying, comments?

DR. SIMON: Well, unfortunately, in that they designed an early RA trial, and the Arava data set was not designed that way, in fact, it limits the observation.

If we're going to be evidence-driven, the evidence we have is that it's early on. In a broader data set, as was the Arava data set, the evidence was clear in both early on and later.

We can argue back and forth to adjudicate this, but, nonetheless, that's what the evidence is.

DR. ABRAMSON: Other comments?

(No response.)

DR. ABRAMSON: So let's take a vote. "To what extent can the radiographic data be generalized to longstanding disease to support a general claim?"

So everyone who thinks it can be generalized, if you could raise your hand.

(No response.)

DR. ABRAMSON: Everyone who thinks it cannot be generalized, raise their hand.

(Show of hands.)

DR. JOHNSON: Maybe I'm misunderstanding what's going on. Let me just ask something.

You're comfortable with generalizing backwards

from bad disease to mild disease to validate a methotrexate effect, yet you're not comfortable with generalizing forward from early disease to late disease? Maybe it's logical or maybe it's scientific.

DR. SIMON: No, not at all. That's why I used the term "Talmudic" in this discussion. I mean, it was an entire construct of assumption.

We don't have assumptions here. We have evidence that in early disease, there seems to be slowing in progression of damage. That's all we know.

DR. ABRAMSON: The language says, "Do the data support a claim for early RA"? Clearly, yes.

Any other comments?

DR. VAN DER HEIJDE: Yes. May I add a comment?

DR. ABRAMSON: Oh, yes. I'm sorry. I didn't see you.

DR. VAN DER HEIJDE: What you can see in the literature, that it's mainly disease activity that's driving if there's radiographic progression or not, and so it's mainly if you have disease, active disease, and if there's early disease or late disease, that's driving, if there's progression or not, and it's not really a difference in disease duration.

DR. ABRAMSON: Lee?

DR. SIMON: Actually, I would take great issue

with that.

There is historic evidence looking at pathologic specimens from patients with rheumatoid arthritis before we had such excellent therapy, where you could actually determine that in non-inflammatory conditions, in patients with pannus that was not driven by inflammatory cells, there was still destruction going on.

One could argue that in the heterogeneous biologic process, that we don't understand entirely what happens, and, furthermore, there's excellent evidence that people will have progression of disease when the disease burns out, meaning that their x-ray evidence of progression gets worse, and yet they have very little evidence of clinical active inflammation.

DR. ABRAMSON: Jeff, yes?

DR. JEFFREY SIEGEL: This issue of generalizability of x-ray findings from early stage disease to later stage disease is an issue we didn't really face when we were drafting the RA guidance document. It's something that has arisen relatively recently.

Given that you feel that the data really don't support a generalization, would you recommend or could the committee comment on whether it would be desirable to have a separate study, separate data, in early versus late or whether we should recommend the sponsors include later

stage patients as well as early stage patients in x-ray trial?

DR. ABRAMSON: It really does create a Catch-22 for the corporation, because we've always wanted early studies, and now someone does an early study, and you say, well, you limit your indication to early disease.

I don't know how to answer. It's always easy to say do another study, but I don't know what the answer is.

DR. SIMON: Well, actually, this is really inherent to the problem that we're confronted with.

The company, as I understand it, was driven by two different questions. The first was they wanted to get approval for early use. They were limited in that, at least from a managed care point of view, and, unfortunately, I think they came with both that question, and they designed in the same trial this other question about structure, and, unfortunately, I would not have designed these two questions together to be answered by the same study. That's not what I would have done.

DR. ABRAMSON: Dr. Garrison?

DR. GARRISON: Just a couple of points.

I think that if you look at the patients enrolled in our trials, initially, they were all less than three years of duration of RA.

We have two-year data, a data set that will be complete in a month. So you can look at those patients at the outer limits here of being of five years' duration of RA, and this is within our one large, very complete data set.

I think I'm not as familiar with the Arava data set as many of you are. There were differences in disease duration in those trials. They ranged from 3.7 years to about 7 years' disease duration, and the label there does not exclude very early use, and I guess the underlying -- well, I guess I'm having a difficult time with this, showing the consistency of the clinical response in all of the studies that we've done, peds, you name it, longstanding disease, very short disease.

We've shown that we have the same clinical effects here, and it is a leap to think that you'll have the same kinds of radiographic effects, but I do believe that the disease is linked, clinical and radiographic activity is linked.

DR. ABRAMSON: Right. I think that's an important point, and I think what Dr. Simon was getting at is that we don't know what disease at 15 or 20 years is like in terms of its responses. So we presume it would be likely to respond similarly.

I think the agency should just understand that

this vote reflected the way this language, this question -- we were asked a very simple question -- "Can this data be generalized?" -- and we answered no.

I think how this label comes out is a different question that ought to be in the discussion between the sponsor and the agency, and the Arava database and labeling, I think, is a model. I'm speaking for myself right now.

I think we were responding to a very directed question, and I think this other discussion is much more complicated, and it should go on separately.

DR. SCHWIETERMAN: Yes. I apologize if this is somewhat confusing.

Clearly, we have to have collaboration with the Center for Drugs, and we do that anyway with many, many things, and I think we'll take this advice to collaborate and work out a meaningful and fair comparison between the product.

DR. ABRAMSON: Okay. I want to thank the sponsor and the committee and everyone here.

We will reconvene for a closed session at 2:30.

(Whereupon, at 1:50 p.m., the open session was adjourned.)