Question number one is on the safety of the agent. The FDA has identified the following adverse events observed in the tocilizumab clinical development program as being of potential concern: Serious infections, liver enzyme abnormalities and lipid parameter changes, gastrointestinal tract perforations, demyelinating disorders. Please discuss, A, the clinical impact of these adverse events in the patient population; B, the need for monitoring; and, C, the impact of these adverse events on the selection of appropriate patients for treatment.

This question is open for discussion. First, the clinical impact of these adverse events: Serious infections, liver and lipid abnormalities, gastrointestinal tract perforation, and demyelinating disorders.

Let's take infections first. Any comments on the Committee regarding the

infectious adverse events seen in these studies? And concerns? Dr. Hoffman.

DR. HOFFMAN: My concern is not with anything that we saw within the data, but the data that we don't have. And this relates to the acknowledge small numbers of patients who are over 75 years of age. While I'm also very impressed with the utility of the agent, its efficacy, and relative safety profile, I still have concerns about the uncertain risk in patients greater than 75 years old.

I'm also concerned about the possible risk -- even though looked at subsets, we really were not informed about those patients -- and the numbers that were within the trials who had chronic obstructive pulmonary disease. We heard -- I believe there was reference to there not being an increased risk of pulmonary infections in those individuals, but we never spoke about the numbers or saw specific data regarding patients who had chronic lung disease. So

unless we have data that speak to that, I would advise caution in the labeling of this agent, should it be approved, in regard to that subset, unless there was data to be presented that we have not yet seen.

DR. WILLIAMS: Dr. Sandborg?

DR. SANDBORG: In addition to very similar comments to Dr. Hoffman, the increase in herpes infections or reactivated viral infections seems unusual for this class of drugs, and I think that we should consider that more for post-marketing studies -- what the implications of that are.

DR. WILLAMS: As to the clinical impact, do we see anything in this agent that is more alarming than in the other biologics we are dealing with? Dr. Sandborg?

DR. SANDBORG: Are we still talking about infection here?

DR. WILLIAMS: I will take the lack of comment as -- Dr. Felson?

DR. FELSON: I don't think there's any

data here that would alarm us more than TNF blockers or other drugs that now are available to us. The one difference I did see -- if you look at their slide P81 -- I mean, so the recent data on TNF inhibitors and infection from the biologics register suggests that the occurrence of that event tends to be relatively early in the course of treatment. You sort of know the people that are going to do this in the first few months. And after that, if they've survived the first few months without an infection, they're not going to have one.

The thing that concerns me about this particular treatment is, it looks like it's just continuous. There isn't a sort of safety period that you reach after a while. I'm not sure that really matters, but I guess it's just noteworthy that there's somehow this ongoing risk that might be a concern.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: David, I think that's a very good point, and well-taken. I will say

that my understanding is that that phenomenon you're talking about, that the risk of serious infections is high in the first six months and then goes down, has been mainly observed in observational epidemiologic studies. I don't believe we've ever seen that in any of the clinical trials. I don't know exactly what that means, but I know Jeff Curtis saw that, and it was seen in the German registry as well. But we haven't seen it when we've looked at clinical trial data.

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: But Jeff, wasn't the meta analysis done at the Mayo Clinic consistent with the emergence of those events right after the start of therapy -- consistent with what David is -- but within the trial data it was seen early.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: So what Dr. Weisman is referring to is Baumgart's meta analysis that looked at malignancies and serious infections in

the safety database of randomized trials for TNF blocking monoclonals adalimumab and infliximab, and it showed a higher risk of serious infection. There are indeed randomized trials of those agents that have seen a higher risk early on, but that meta analysis didn't compare the early experience with subsequent experience, as far as I can recall.

DR. WILLIAMS: Do we see a need for monitoring over and above that mentioned by Dr. Hoffman as post-marketing surveillance? Dr. Hoffman mentioned the impact it had on elderly patients.

Is there an impact in this specific areas of adverse events -- infections -- on our selection of appropriate patients, other than possible consideration of age?

Dr. Hoffman?

DR. HOFFMAN: We didn't address the chronic lung disease as well, and their increased likelihood of infection. In general, is that aggravated by not just this biologic,

but really any biologic, which I don't think we've addressed in these sessions in the past.

DR. WILLIAMS: Do you wish any more information on this particular area? Let's move on to liver enzyme abnormalities -- concerns of the clinical impact of this on the patient population. Dr. Pisetsky?

DR. PISETSKY: I'm not sure it's a concern, but I think there are going to be practical issues of how you assess it over time, especially in people who are on methotrexate. Since methotrexate itself can cause liver abnormalities, I think the question is, what is the appropriate time after the dosing of this agent, after the dosing of methotrexate, to make this assessment?

I always wait days after someone takes methotrexate before I look, because I know there's an immediate dose-related effect. So I think one thing that would be useful is specification for the time when the assessment should be made, and I think that

would clarify this issue.

DR. WILLIAMS: Dr. Blumenthal?

DR. BLUMENTHAL: I believe we also have to keep in mind that many of these patients are going to be on statins at the same time they are possibly on this agent and also on methotrexate, which adds an additional layer of complexity that the clinicians are going to have to watch.

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: I think the issue that is raised is monitoring, and how frequent should the monitoring be? I think the vigilance that's suggested with the monitoring is appropriate -- you know, what to do when you see it. That's based upon the trial data, where they've had experience. And of course, within trials the patients are monitored every two weeks, every four weeks. What do we do in practice when it comes to monitoring these patients with this drug? I think this is a real serious issue. Right now, the recommendations

for methotrexate monitoring are anywhere between six weeks and 12 weeks, depending on what side of the country you're on. Should the combination be monitored more frequently than six to 12 weeks? This data seems to indicate that it should.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: I guess the other issue about monitoring is where albumin fits in, since we're going to be looking also not just for the hepatitis, but theoretically interactions with methotrexate in terms of hepatic fibrosis, which we did not discuss -- how that monitoring should fit in.

DR. WILLIAMS: Do we have a recommendation on the need for monitoring and how we should recommend monitoring? I had the impression from the sponsor they were recommending it at each infusion.

Dr. Krasnow?

DR. KRASNOW: Joel Krasnow from Roche. Our recommendation was that we monitor hepatic

transaminases four to eight weeks following initiation, and then based on the initial results, monitor them as clinically indicated.

DR. WILLIAMS: I think we need to make some recommendation of how often we think that would be clinically indicated, particularly in the face of methotrexate therapy.

Dr. Fletcher?

DR. FLETCHER: Maybe just to put a question: Would the typical monitoring for methotrexate be adequate except during the initial three to six-month period of initiation of this drug, where you might want to monitor more frequently, as a proposal? I don't know that there's any said way to do that, but something a little more concrete like that?

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: I was just going to say some of this really depends on how often you're going to monitor for methotrexate, and is there any reason to believe this would exacerbate the hepatic risks from methotrexate, which would

suggest more monitoring, at least initially?

DR. WILLIAMS: What about the patient who receives this as monotherapy?

DR. WEISMAN: Well, Jim, what do you think about this? You've had some experience with methotrexate and liver toxicity issues, and it's been discussed with you, and your colleagues have published on this over the years. What do you think?

DR. WILLIAMS: Well, I don't know which side of the country you consider me on, but I do methotrexate every 12, and that may not be often enough for this drug. I think -- my own opinion, looking at the data we've seen here is, I'd probably do it at least every other infusion if they're doing it every four weeks.

DR. PISETSKY: I'd say that's reasonable, as you extend it into different patient populations outside the trial setting, to be conservative; to get more experience rather than just saying every three months or every other infusion, because these are going to

be on people who are potentially on more than one hepatic drug. Some are going to be on NSAIDs, some are going to be on methotrexate, plus this agent, plus other things. And I think initially it would be prudent to probably monitor more cautiously initially, and then go to maybe whatever is dictated by methotrexate, for those on methotrexate, and then maybe every other infusion for the others.

DR. WILLIAMS: But I think it should be outlined, because in private practice they don't monitor, perhaps, as closely as we do in trials, so that it should be stated how often it should be done, so the practicing physician has a guideline. Dr. Sandborg?

DR. SANDBORG: I think that the recommendation of doing it -- if you're using it in combination with methotrexate or perhaps other liver-toxic drugs like statins, or high doses of NSAIDs, or whatever -- should be every month to every two months, and then continuously even every two months as long as they're on a

liver-toxic medication.

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: Jeff, a question, and maybe Sarah too. It seems like the FDA has not mandated that this drug be tested in large open-label experience for safety prior to coming today to the advisory Committee, where thousands of patients with a variety of drugs, concomitant therapies, and so forth are -- like we've seen with some of the other agents that have come to the FDA. What's your thinking behind that? And it comes up to this issue now that Dr. Pisetsky just raised about if you're trying to think about monitoring, and the drug is going to be out there, and it's going to be out there in a variety of circumstances in different patient populations with different concomitant medications, different risks, and so forth -- we don't have background experience in that right now.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: So this is a concern that

we've had over the years, and we've generally recommended to sponsors that they do a large randomized study of all comers, as it were -- patients on a variety of concomitant medications, with a variety of concomitant medical conditions, and then add either placebo or drug to it, and then to roll those patients over into a long-term open-label treatment study. This was a design that was used with anakinra, with abetacept.

So we have seen this with other agents. This was -- the intention of the trial that was done with this product, where it was added to concomitant DMARDs, so there was an experience. I think that that is the trial that's intended to satisfy what you're talking about.

DR. WEISMAN: Are you satisfied that that experience with the number of patients here and -- both of you guys -- that in part answers David's issues?

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I think that the study enrolled patients on a variety of DMARDs that are used in practice. Of course, it excluded other biologics, and we don't feel it's appropriate to use this with other biologics until that's formally studied. But it was used with a variety of conventional concomitant DMARDs, so we do think that that issue was addressed.

In terms of whether patients with concomitant medical conditions like COPD, or as Gary Hoffman was wondering about, diabetes, and some of the other concomitant medical conditions, it may be that we don't have as much information as maybe it would be nice to have as patients are treated more broadly.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: I have a question about the interpretation of the patient who obeyed Hy's law. Has there been another biologic in which a patient fulfilled Hy's laws in a

way -- because if that's not the case, that could be an indicator of hepatic problems. I can say caution is indicated.

DR. WILLIAMS: Dr. Sandborg?

DR. SANDBORG: I think this, as in many of the other questions and the areas we'll be coming up with, is going to be hopefully answered by the registry studies, where you have a more real-life situation, where you may be using different doses of different combinations of drugs. And I think that that will be helpful, but even though there's many patients in these studies, these are still low signals that we need to look vigilantly for, especially the liver, I think, and the intestinal perforation.

DR. WILLIAMS: We'll get to the latter in a minute. Dr. Weisman?

DR. WEISMAN: I think to answer your question, Jim, the sense of the Committee to me is that the sponsor's recommendation, which is to monitor once at four to six weeks or four to

eight weeks, and then when clinically indicated, is probably not sufficient now. But what is sufficient --

DR. WILLIAMS: Certainly in the face of methotrexate therapy.

DR. WEISMAN: Yeah, and that's -- and what is sufficient -- what is -- is it six weeks? Is it every other infusion? We don't know the answer to that. But I think that the FDA should weigh in on this as well as the Committee -- and I don't know whether we can come up with a number -- but the current thought of once and clinically indicated does not seem to be sufficient.

DR. WILLIAMS: I would have probably said every six weeks, except that they come for infusions every four, so why make them come for a separate visit? So I settled on eight. Dr. Pisetsky?

DR. PISETSKY: Is there an agency guidance on a product where Hy's law is met, or there is a patient who fulfills Hy's law? Or is

it just judgmental?

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: So the question you raised before. So I'm not aware of another case of Hy's law with another biologic in a clinical development program.

DR. PISETSKY: What about any product that has a case that fulfills Hy's law -- for any kind of product?

DR. WILLIAMS: Dr. Rosebraugh?

DR. ROSEBRAUGH: There are -- when we get Hy's law, the thing that it gives us, as we tried to point out in the slides, is that it gives us some indication of what the rate of severe liver toxicity might be, and that helps us to try to weigh that against the benefit of the drug. Are there other drugs that fulfill Hy's law? Sure, there's lots of drugs out there. Most of them are treating very severe illnesses kind of like this one. We recommend a lot of monitoring on them.

We know what the rate is, so we

look for it specifically. Are there other drugs that have had Hy's law that we didn't approve? Sure, but they were drugs that were treating things that were not quite as serious. We had other drugs on the market that were just as good. So Hy's law in itself doesn't kill a drug; it just gives us an idea of what the rate may be and how close we need to monitor it, and maybe some idea of how it compares to others on the market.

DR. PISETSKY: Could you be more specific on how close -- I guess the question is how close to monitor is --

DR. ROSEBRAUGH: Yeah, that's really what we're asking you guys, and we'll go back and talk about it, but we certainly respect your opinions.

DR. WILLIAMS: Is there an opinion difference on the one Dr. Weisman and I have stated?

Every other time, every eight weeks?

SPEAKER: Forever.

DR. WILLIAMS: Personally, we keep doing it.

SPEAKER: Forever.

DR. WILLIAMS: Especially if they were on methotrexate, I'd just -- because I monitor methotrexate anyway.

Dr. Blumenthal?

DR. BLUMENTHAL: Obviously, this is something that we'll continue to review as data comes in. As we all recall, there was a time when we did liver biopsies in patients on methotrexate, and upon further review it appeared to be unnecessary. So I think erring on the side of caution at first, and perhaps being less cautious if the data suggests that that would be safe, is something we could consider as time goes along.

DR. WILLIAMS: Excellent comment. It's not immutable. We can change it when the data comes. Does the liver enzyme data have an impact on the selection of appropriate patients

for treatment, above what the sponsor has already recommended -- we don't treat patients with chronic liver disease?

Dr. Pisetsky?

DR. PISETSKY: I mean, clinically, one of the major issues is people with hepatitis C, and that's not a small number of patients. It's a question for any biologic. If you already have a product that may have a hepatic signal, I think there would be concern in the absence of data.

DR. WILLIAMS: Any further comment on liver function abnormalities? We come then to the interesting topic of lipid abnormalities. Dr. Felson, you had some opinions on that.

DR. FELSON: Well, I guess to be honest with you, I wasn't especially reassured by the expert from industry. I think there's no obvious -- it sounds like the effect of other biologics is to increase HDL and LDL, the HDL effect being substantial. There is no substantial HDL effect here; this is an increase

in LDL. This increases risk, and I'd be nervous about it. And I think the nervousness is especially because most of our patients are older patients, and this is the disease that's unfortunately going to kill them -- cardiovascular disease. So the extent we increase that risk, it's a problem. And I think if we approve it, we need to be clear that -- I think people, probably, who are either on treatment for or have LDL elevations or total cholesterol elevations that's concerning clinically probably ought to not get this drug. Or there ought to be a warning.

DR. WILLIAMS: What if they respond to statins?

DR. FELSON: I mean, the problem is they're going to be on statins the minute -- they're already on statins, assuming, so if they're well cared for and they have hypercholesterolemia of some kind, they're going to be on statins there. And we don't know, necessarily, how this plays out in that context.

So I guess there needs to be some kind of warning. It's hard to know exactly how to phrase it, because statins might do it. But I guess I'm also nervous about the idea that the problem's going to be discovered and then the patient's going to be started on statins. I mean, you know, that they could use one drug to treat the problems introduced by another is a concern.

I can foresee the possibility that in five years there's another hearing like the one on Vioxx, where the cardiologists actually in the room this time, the academic cardiologists, which they aren't this time, other than maybe one, and they say to us, what were you guys thinking when you approved this drug? And so I'm nervous about that.

And I think I would also say to the FDA, if lipid abnormalities are going to generate a concern on the part of any drugs that we're going to approve, or anything that's cardiovascular risk-related, that it

would be helpful around this table to have somebody who's an expert in that area that can advise us, because I'm nervous about a lot of the extrapolations I'm making, frankly, because I'm not a lipid person. But the lipid that's being made abnormal here is not a good one, and I think this is a high-risk group, so I'm definitely nervous. And I don't know whether it should preclude certain people from getting this therapy; I think it should clearly introduce monitoring of LDL as a routine. And whether that's the same schedule as we just talked about for LFTs I don't know.

DR. WILLIAMS: Dr. Blumenthal?

DR. BLUMENTHAL: I think one of the things the Committee is grappling with here is, we want to try to protect the safety of the public, but a lot of what we're assessing here are surrogate markers for the actual thing that we want to know. We want to know if our patients are going to have heart attacks or

strokes, but it takes a study of such size and such a duration of follow-up that we might not have that kind of data at the time we have to consider this question. So we consider the surrogate markers, which are easier to measure in a shorter time frame, but we don't always know what it means when one surrogate marker moves in what appears to be an unfavorable direction -- and I don't know that we even know that for sure -- and another surrogate marker, such as CRP, moves very strongly in a favorable direction. So what does that mean?

The cardiologists would argue that CRP is an excellent marker of short-term coronary risk, and I don't think anybody really entirely knows yet -- what if you chose that risk factor and tried to modify it, what would your coronary risk be then? The cardiologists don't have the tools to do that, so I don't think we have data to answer that question. So we have one surrogate marker moving in one direction, another

surrogate marker moving in another direction. It is possible that coronary risk would go up if a patient was on this drug. It is also possible, I would submit, that a patient's coronary risk could go down.

And I think Dr. Siegel's approach actually is a very sensible approach; that since we're getting no red flags so far, based on preliminary data, of the actual endpoint that we want to know, which is a coronary event, that maybe studying the question and accumulating data as we go along, and being aware that we might have to act if unfavorable data comes in, is the way to go.

DR. WILLIAMS: Dr. Hoffman?

DR. HOFFMAN: Dave Blumenthal just addressed the point I wanted to make, and I'm more comfortable with that approach than putting a warning or restricting the drug for use from those people who start out with high LDLs. I don't know enough about the data, but perhaps

other people on the panel do, in regard to risk of coronary artery disease in rheumatoid arthritis. I didn't believe that that risk was clearly related to increased adversity in terms of lipid profile as much as active inflammatory disease, which appears to be the case in other chronic inflammatory diseases as well.

DR. WILLIAMS: Dr. Felson?

DR. FELSON: Yeah, I think we're going to argue about something we can't know the answer to for a while, and there's just not enough data to know. I think we ought to probably have guidelines that allow us to get lipid information in the future, in addition to event information. And if we don't do something that asks people to collect these data, we won't know. And I'm nervous about that.

I think we can sit here and argue about what risk factors there are in rheumatoid arthritis for cardiovascular disease, and I don't know that that's going to get us a whole lot of places. I think

there's enough concern here -- I don't disagree with Jeff's comment -- but I think just collecting data and collecting data may not be the same thing; that if you say, look, we need to get data on what happens to lipids and other factors that might affect cardiovascular disease so we can not only figure out how many events there are, but we can understand what's going on here, because it took us a long time with Vioxx to recognize that there were enough events, and a number of people died as a consequence.

I think to the extent that we can know that there are particular problems in some people whose lipids go very abnormal, and maybe some of those people turn out to be at risk, I think it protects the community a little than if we do nothing.

DR. WILLIAMS: One comment, and then I'll turn it over to Dr. Pisetsky. The elevations were not enormous; they were abnormal, but they were not enormous.

DR. PISETSKY: Yeah, I agree with the idea of monitoring, but I think it's going to be important to have an appropriate control group. The spectrum of RA has changed dramatically recently. There are much higher numbers who have high BMI with metabolic syndrome, with other cardiovascular risk factors. So to assess the impact of this agent, you would need an appropriate control on it. I will leave it to you to figure out what the appropriate control is, but I don't think we can rely on old numbers.

DR. WILLIAMS: I think they're going to ask us for a recommendation on monitoring. Dr. Weisman?

DR. WEISMAN: I think Dr. Blumenthal said it best: When you have a paradoxical situation where you have Framingham risk factors going up with a drug, hypertension, lipids, and others going down, like CRP, and then you have control of inflammation, and you have these overlapping circles, where are we at this point?

And where should the burden of proof be right now? I don't think there's enough information about this paradox to restrict how this drug is going to be used if it's approved, except to collect the data. And collecting the data is what I think David and David both said, how to do that. We can make some recommendations to the FDA, and I think we should.

DR. WILLIAMS: What does the practicing physician need to do to monitor for this problem, because he's not going to be collecting data?

DR. FELSON: One of the things that was said repeatedly was, if the lipids go up, you can just start statins. And I think that begs the question of how do you know if the lipids go up. And I think the concern might genuinely be that if the lipids go up, the LDL especially, without any HDL concomitantly rising, and you do nothing about it, that you put the patient who is otherwise at high risk at higher risk. And I think the reasonable thing

to do might be to build in some monitoring protocol that -- and this doesn't need to be as frequent as the LFT protocol -- but I think probably doing some kind of monitoring of this is reasonable, so that we can avoid problems in the future.

SPEAKER: How often?

DR. FELSON: Oh, thanks. I don't know.

DR. WILLIAMS: That's the question they're asking us.

DR. PISETSKY: But if this is not different than any other biologic, or different than anti-TNFs, what --

SPEAKER: That isn't necessarily the case.

DR. PISETSKY: Is that true or not true? We've heard that this is like anti-TNF, where cholesterol monitoring, as far as I know, is not required, or LDL monitoring.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I don't believe we've

seen a head-to-head comparison of the two, but we haven't identified increased lipids as being a safety concern with the TNF blockers. The signal is not as clear as it has been with --

DR. PISETSKY: Not as clear, so the data we heard you would not agree with exactly?

DR. SIEGEL: Well, I'd have to review that, but we haven't identified it as being a safety concern.

DR. WILLIAMS: Dr. Fletcher?

DR. FLETCHER: Just a fine point, but I put the question to FDA or to the sponsor with regard to a review of the literature. With the TNF blockers there is published data suggesting that you may have increases in lipids. Is the HDL and LDL relative increase similar in TNF inhibitors, or is it imbalanced, and therefore the risk ratio, if you will -- and I'm wondering also whether Dr. Felson would have less discomfort if both the HDL and LDL were increasing proportionally the same.

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I believe that was the question that Dr. Pisetsky was asking, and I haven't reviewed those data, and I'm really not prepared to comment.

DR. WILLIAMS: What is our recommendation to the FDA on frequency of monitoring, not for the investigator, but for the practicing physician? I will throw out one. Oh, Dr. Hoffman, I'll let you do it.

DR. HOFFMAN: Well, I'm going to skirt the question by saying that without having adequate data to prove that an intervention actually makes a difference -- statin, for example, makes a difference -- that we're ill-prepared to make a recommendation; that I would prefer to make a recommendation that was more generic, that goes beyond this panel. That is, people who have risk factors for coronary artery disease, which is all of us, and certainly our older patients, which is the majority of the population with RA, have assessment of lipid profiles and other

cardiovascular risk factors evaluated, as would be the standard of care in general internal medicine.

But to make a recommendation without having adequate data about risk -- we haven't seen increased risk, nor have we seen an intervention that addresses a presumed risk, both of which imply an increase in the expense of health care delivery -- I think would be premature in the absence of appropriate data.

DR. WILLIAMS: What I hear you saying is that the recommendation of the sponsor was appropriate; that lipids be looked at and treated appropriately.

DR. HOFFMAN: Yes, sir.

DR. WILLIAMS: Other comments? Dr. Felson?

DR. FELSON: Gosh, for once I disagree with somebody. I completely disagree with that. So what have -- what I think we're seeing is an increase in LDL and total cholesterol, and

unlike other TNF and biologic agents, no change in HDL -- so we're seeing a cholesterol and lipid panel that increases risk in a group of people we know are at high risk, using a biomarker that has been traditionally and historically well tied to risk in this population. So it's like saying, what do you mean? Blood pressure's increasing; we shouldn't be worried. Of course we should be worried.

DR. WILLIAMS: But I go back to the comments of Dr. Blumenthal. CRP does down. That's going the opposite direction.

DR. FELSON: Well, and I think that's partly why we need to collect some data here. And I think one could make an argument that you don't know what the net effect of theses things is going to be.

But I think we've been burned as a community before in assuming that the net effect is going to be fine, and I don't think we can assume that. I would remind everyone also that we're not in a dire situation where

there's nothing else available for these patients; there's a lot of other things available that are roughly equivalent in efficacy and may not have this cardiovascular profile problem.

DR. WILLIAMS: Dr. Sandborg?

DR. SANDBORG: So I'm a pediatric rheumatologist, so I don't have as much experience in worrying about lipids. But it sounds like one could consider making a more conservative recommendation to the practicing physician during the period of the post-marketing studies, and then come back when we actually have a better idea of what, actually, we're worried about.

DR. WILLIAMS: Dr. Stine?

DR. STINE: Just a small comment about the nature of the data that we do have. We've pointed out that one risk factor goes up and the other one goes down simultaneously. It's important to recognize that's what happens on average. It could be the case that the people

whose one risk factor goes up, the other risk factor doesn't change. It's maybe some people that didn't respond on one that changed on the other. Saying that something happens on average in two groups doesn't say anything about what happens to any individual in those groups, and so it's important to recognize that once again -- and we do have an absence of data that would speak to the relationship of these risk factors going forward.

DR. PISETSKY: I'm concerned about how we'd get the data, because if I already had a patient with an unfavorable lipid profile who's already on a statin, and I have a choice of agents, would I pick one that already has another lipid problem? The answer is probably not, if I have other things to choose from. And the question is, how, in a post-marketing situation, are we really going to get data on real cardiovascular risk events if in fact I would be reluctant to use it in the people at risk?

DR. WILLIAMS: Do you have enough information on this, or do you want us to continue to discuss it?

DR. SIEGEL: I think we've heard a pretty good discussion so far.

DR. WILLIAMS: Now that we've solved the problem with lipids, we'll go to GI perforations. Dr. Weisman.

DR. WEISMAN: I was struck with two things. One is, this drug has a rather unique mechanism of action that we've not seen before in any approved biologic, which was emphasized by the sponsor. And also this signal about gastrointestinal tract perforations. And I'm struck with, is there a relationship between these two things? And I'd like to hear some more discussion about it; speculation about it, at least. We have an expert, Dr. Watkins, who's here as a gastroenterologist, who's told us that he's interested in IL-6 in the GI tract, and mechanisms, and relationships.

Can you enlighten us a little bit?

Is there a potential relationship here between these receptors, receptor blocking, what goes on in the GI tract, and how this could be manifested in patients with a risk, like they already have diverticulitis, for example?

DR. WILLIAMS: Dr. Watkins?

DR. WATKINS: Yes, Paul Watkins. I am a gastroenterologist, but actually --

DR. WILLIAMS: Could you state where you're from, Dr. Watkins?

DR. WATKINS: University of North Carolina in Chapel Hill. But actually have been exclusively doing clinical hepatology and hepatology research. So I could talk quite a bit about IL-6 mechanism in the liver and hepatocytes. I'm not in a position as an expert in IL-6 in the GI tract or the relationship to perforation. Sorry.

DR. WILLIAMS: Dr. Hoffman?

DR. HOFFMAN: We saw in some supplemental slides that were provided in the

discussion of perforation that there were more perforations in patients who were taking NSAIDs, and especially NSAIDs plus corticosteroids. Although the total numbers, the event rate, was relatively low, still the data was compelling, and this led in Hoffmann-La Roche's presentation to recommending that GI mucosal protection be advised for people receiving these drugs, although I'm not aware that GI mucosal protection would have any impact on lower intestinal perforations.

So I, for the moment, would feel more comfortable -- should the licensing be approved -- to have listed as a relative contraindication the use of nonsteroidal anti-inflammatory drugs in patients with RA who are concurrently receiving tocilizumab; until we have more complete and compelling data, for that to at least be a consideration in the labeling for the product.

DR. WILLIAMS: Other comments?

Dr. Sandborg?

DR. SANDBORG: In looking at the materials, the risk of perforation in RA is actually highest with corticosteroids, so I would second that, but actually I would focus more on the corticosteroid issue than on the NSAIDs.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: I was going to say I don't know that I've seen a perforation in someone with RA, and so I must say that I'd be concerned by these data. We know their effects on white cells. We've heard about neutrophils, their effect on clotting factors. We know the acute phase reactants, all of which can affect the healing process. And so I wonder about people with prior GI events, prior diverticular disease, and other events that already occurred, and how you would use it.

DR. WILLIAMS: I trained a long time ago, but one of the things I was taught is that abdominal pain in an RA patient with steroids was a bowel perforation.

DR. PISETSKY: Yes. In fact, if they came to the ER, I said that's the first thing to look for. Look for air in the abdomen. That's how far back I go. Actually, I was going to say the patient was on gold.

DR. WILLIAMS: Other comments? This was a complication that was little increased, but I don't know if it's been looked at in other areas.

DR. WEISMAN: I'm curious how the FDA views this. Are there other databases, or other ways we can examine this question, because it's brand new, these perforations, and it stands out like a sore thumb. And I'm concerned.

DR. SIEGEL: Jeff Siegel. This actually was not the first time GI perforations have come to our attention. We saw cases in the post-marketing of spontaneous adverse event reports for TNF blockers, and in a review of the literature it turns out, as Dr. Williams was saying, that this is a recognized complication in RA. And when people have looked into it,

there are a variety of different potential mechanisms, including NSAIDs and steroids sometimes. Sometimes they find vasculitis in these cases. It's very, very unusual, but we have certainly seen it in adverse event reports in RA populations.

DR. WEISMAN: Jeff, do you think there is a high-risk patient for such a complication?

DR. SIEGEL: Apart from what I mentioned about the case reports being mostly people on NSAIDs or corticosteroids, I'm not aware of other risk factors particularly.

DR. WILLIAMS: I think we're kind of in the same situation we're in here that we lack long-term data, and that we know it occurs and it's a risk with steroids. Do we think this drug increases the risk?

Dr. Sandborg.

DR. SANDBORG: I just have a question. With the use of the TNF inhibitors in inflammatory bowel disease, is there any increase there that is seen?

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: I'm not aware of one, but don't quote me.

DR. SANDBORG: It's interesting that this drug isn't being looked at in inflammatory bowel disease, as so many of the other ones have been.

DR. WEISMAN: Of course, the TNF drugs actually heal perforations and fistulas and things like that, so how do you deal with this phenomenon?

And I'm thinking to myself, well, let's say we are concerned about it, which we are. What kind of warning, what kind of statement, what kind of comments should we recommend to the FDA to discuss with the sponsor about labeling issues? How do you know who has a history of diverticulitis? How do you know that? So it's not an easy question to address.

DR. WILLIAMS: Dr. Hoffman?

DR. HOFFMAN: I'm going to ask Jeff to

recall some of the deliberations over the NSAIDs and the COX-2 inhibitors when we spoke about them. Our concerns for cardiovascular risk were great enough, and then later we broadened our concerns to also renovascular risks, so that I think the general recommendations for the use of NSAIDs as a class is to use the lowest effective dose for the shortest possible period of time. So here in RA we are treating patients in polypharmaceutical fashion.

We have some data that low-dose steroids actually does change the course of the disease in terms of erosive destructive disease. We have no such data for NSAIDs, and we already have warnings on NSAIDs that suggest again lowest possible dose for shortest period of time. So I think it's compatible with those notions to have within instructions to patients that NSAIDs are known to be a risk factor for gastrointestinal perforation.

There was, as Christy pointed out,

an increased risk also for corticosteroids. I'm not sure it's higher than NSAIDs because we only saw the NSAID data in the supplementary slides. But all of the people who had lower intestinal perforations -- I think it was the lower intestinal; I could be corrected on that; maybe it was the upper intestinal -- they were all, all on NSAIDs, six out of six, I believe. Upper.

So I think, to be consistent in our labeling for NSAIDs, and in this case NSAIDs in conjunction with a drug that may or may not increase the risk of gastrointestinal perforation, we should re-emphasize that the combination of this agent with NSAIDs, or even more than minimal low-dose corticosteroids, is at this time of concern and under further investigation.

But I think practitioners and patients in the instructions that are issued, the labeling, have to be reminded of this combination risk.

DR. WILLIAMS: Further comments on GI perforations?

Dr. Sandborg.

DR. SANDBORG: So I think this goes back to Dr. Weisman's comment about mechanism. This is a different drug, and also IL-6 is, and IL-6 receptors are, probably widely distributed on the GI epithelium, sort of different than some of the other biologics we've worked with. So I think that we do need to be very cautious and somehow vigilant, but the question of how to do that is -- the devil's in the details.

DR. WILLIAMS: Other comments? Do you desire more?

DR. SIEGEL: No, that's good, thank you.

DR. WILLIAMS: Moving from one foggy area to another, we'll go to demyelinization.

Dr. Blumenthal.

DR. BLUMENTHAL: I wonder if Dr. Siegel or Dr. Rappaport could help me out, but I think one of the difficulties we're having

here is, we don't really know what the baseline prevalence is of demyelinating disorders in patients specifically with rheumatoid arthritis. And if I'm remembering this right, this has been a clinical issue since the first TNF inhibitor was approved, which was approximately 1one years ago. Demyelinating disorders can be difficult to diagnose, and interpretation of MRIs of the brain can be difficult, especially in older adults. Can you help me out with understanding why it's been so difficult to get data on a comparator group or a control group?

DR. WILLIAMS: It's hard to deal with this one, since we haven't even decided cause and effect with the others.

Dr. Siegel?

DR. SIEGEL: I can make a couple of general comments that may be helpful. You all are trying to come to grips with issues that are new, and where we don't really have all the information that we need to make firm conclusions. And this comes in part from the

fact that we're asking companies to collect much larger safety databases than we ever have before. When you expose patients to drugs for long periods of time, you uncover events that may be part of background events in that patient population, and it becomes difficult to sort out what's due to the drug, what's due to the underlying patient population, especially when the events occur in the long-term open-label treatment.

So we understand the difficulties in dealing with this, and we're asking for your help, based on your clinical judgment, in guiding us as to what you feel.

With respect to the demyelination, the situation is a bit different than with the TNF blockers. It is true that we saw demyelinating events with the TNF blockers shortly after they were first approved -- the initial ones, Remicade and Enbrel. But we had additional information that could help us. It was a prospective study of

infliximab, where the first three patients had worsening in their CSF parameters and in their MRI.

And we had a randomized trial of a TNF blocker that was never approved that showed a shortened time to multiple sclerosis flare on treated patients than in placebo controls. Those data let us feel that there was a clear evidentiary basis for being concerned about demyelinating events with TNF blockers, and that was part of the basis for making the warnings.

Here it's a bit different; these events occurred in the total database. We don't really know what the underlying rate is, and we don't have a control for that since they occurred in the open-label extensions. That said, I think we have a little bit of information on the background rate.

DR. WILLIAMS: Dr. Rappaport?

DR. RAPPAPORT: I was able to get a

little bit of information from the MS Society. The incidence appears to be about one in 30,000 in this country, and so that was calculated based on an occurrence of 200 new cases diagnosed a week.

DR. WILLIAMS: Do we have any information on what that is in a chronic inflammatory disease?

DR. RAPPAPORT: Well, I could check that again, but it's not a number that I have in my head.

DR. WILLIAMS: My impression is it's higher in the rheumatoid population. Dr. Hoffman?

DR. HOFFMAN: For imaging studies taken in people who were not suspected to have any indications of a demyelinating disease but had an MR done for other purposes like trauma, there must be thousands of MRs done every year in the United States for trauma, seizures, severe headaches, but not real suspicion of demyelinating disease. And because the findings

can be non-specific, I wonder if that would be a reasonable control group to compare when one looks at this population?

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: Well, when it's all said and done, I don't see a signal in this data that we're dealing with something that's unique or special, so I don't --

DR. WILLIAMS: Different than other biologics. There's a signal, but it's no different than other biologics.

DR. WEISMAN: Yeah, I think we have other fish to fry here, so -- or whatever the expression is -- I don't know.

DR. WILLIAMS: Other comments? That sounded rather conclusive, so -- are we okay with safety for you?

DR. SIEGEL: Yes, thank you.

DR. WILLIAMS: Question number two. Three of the five studies submitted in the application contain data on tocilizumab 4 mg/kg in combination with methotrexate. These data

demonstrated a statistically significant increase in the proportion of ACR 20 responders in the tocilimi -- tocil -- the drug 4 mg/kg treatment group compared with the placebo, although the proportion of patients achieving this response was lower than that observed with the tocilizumab 8 mg/kg treatment group. Regarding safety, the 4 mg/kg dose appeared to be associated with a lower incidence of serious infection than the 8 mg/kg dose, when used in combination with a DMARD.

No GI perforation events were reported in patients on 4 mg/kg. In the 24-week control period, three GI perforations occurred in patients on 8 mg/kg compared to none on placebo or 4 mg/kg. The sponsor has proposed a dose regimen of 8 mg/kg every four weeks. If tocilizumab is approved, do you agree that this is the appropriate dose?

Discuss whether there are patients at higher risk of adverse events for whom a lower dose should be recommended.

Dr. Felson.

DR. FELSON: Yeah, I was surprised, I think as indicated by my questions to them, that that was the dose they selected. I mean, if you look at their slide P39 -- so the ACR 20, which is the primary outcome we're all talking about, is a composite measure that's determined by a variety of outcomes, including CRP or ESR, and this obviously has a tremendous and very favorable effect on CRP, especially when used at the 8 mg/kg dose, not so much at the 4 mg/kg dose.

When you give 4 mg/kg, the other outcomes look like they do just as well as -- the non-CRP outcomes -- I think they do just as well as when you give 8 mg/kg. And those include the ones that are important to patients: Tender joint count, pain, patient DAS, and HAQ score. This looks pretty effective to me at 4 mg/kg.

I was having more trouble than this slide indicates coming to grips with whether

there was less toxicity with that lower dose. You know, one always thinks there's going to be less toxicity, but the data wasn't all that clear to me. But I did think the data was pretty clear in suggesting that the 4 mg/kg dose was effective. And I couldn't see why that couldn't be used in some people who are going to have trouble clearing that med, or in ways that we often do, giving it at a lower dose to older people who might be at risk.

DR. WILLIAMS: My concern had been that if we gave a lower dose, would they develop tolerance and not respond to the higher dose? But the data that they showed showed that those on 4 mg that they subsequently gave 8 mg had a similar response to those that were started on 8 mg, so I personally think you could start with 4 mg and increase to 8 mg if they didn't get adequate response. And I differ a little; looking at the data, I thought there was a little less toxicity on 4 mg, but not a great

deal.

But there was some less. But I always am a believer in less is better.

Dr. Weisman.

DR. WEISMAN: I think David's comments now really are extremely appropriate to the situation, looking at both benefit and risk. I think he's cleared the air for us. And I don't see why this shouldn't really go in the other direction, that patients should be started on 4 mg, and if there is a need -- a demonstrated need, for whatever clinical indications -- that 8 mg would be available, recognizing that the data indicates that there's perhaps a slightly higher risk associated with 8 Mg/kg. So it seems fairly clear-cut.

DR. WILLIAMS: I don't know how the company's pricing it, but you would think that it would cost less also to start with 4 mg.

DR. PISETSKY: I would agree, especially if you look at something like the DAS, which is going to be very sensitive to sed

rate and CRP. I mean, they have the data to look at tender and swollen joint counts to see if there's really a difference in such a measure as that. If there isn't, then I would think prudence would say 4 mg. It's a lower dose, it's better safety, and you're going to get the vast majority of the response that you'd get at 8 mg.

DR. WEISMAN: Let me ask you: Isn't the SDAI the one that does not include acute-phase proteins?

DR. PISETSKY: Yes, or there's a CDAI and an SDAI that --

DR. WEISMAN: One of them does not. I'm curious as to whether there was a difference -- if they were measured, and was there a difference between the two doses?

DR. PISETSKY: Well, they have it, because it's tender, swollen, patient, global, and physician. They might, they might.

DR. WILLIAMS: I don't see a lot of disagreement among the Committee. I would be

interested, before we go to a vote, if the patient advocate or the consumer representative have any specific comments they'd like to make on the safety or efficacy of this drug.

MS. MALONE: Well, I think less is more, you know -- to start out lower because you can always go up. And I would agree with what they said.

DR. WILLIAMS: DO you have any specific concerns about the safety?

MS. MALONE: The GI bleeds bother me. And I -- shades of the past -- I remember with COX-2, you know, that was the big deal, that it was supposed to not have that as a problem, and then they did. And here we know that they are.

DR. WILLIAMS: Ms. Aronson?

MS. ARONSON: Yeah, I'd like to just express the concerns about safety as well regarding infection and cardiovascular risk as well as the GI perforations, and also the neutrophil drop in relationship to infection as well. I also have a concern about the

concomitant therapies and not enough data, so I have a concern about that and other diseases such as COPD and diabetes.

DR. WILLIAMS: Dr. Blumenthal?

DR. BLUMENTHAL: I agree with everything that everyone has just said, but I would like you to take a look at slide P54 just for a moment, which is the discussion of the efficacy of this agent in patients who are TNF non-responders. I see this as the group who realistically is going to be getting this drug, at least in the near future. I think the safety and efficacy data of the TNF inhibitors, and just the huge numbers that we have that enable us to have confidence when we speak to safety and efficacy, suggest that in our practices we're probably going to be going with TNF inhibitors as our first biologic, and we wouldn't be considering this agent until we were considering a salvage therapy later on in their treatment.

So the data that specifically

speaks to how a TNF non-responder would do when on this agent I think is relevant to the decisions that we're going to make. And I completely agree that going low, going slow, and being cautious is the way to go, but if you look at the ACR 20, 50, 70 numbers for the 4 mg/kg dose, they're not impressive numbers.

If somebody told me a biologic got 30, 17, and 5 for their ACR 20, 50, 70, I don't consider that a particularly impressive response, though admittedly this is a tough group of patients, and they might be a little more refractory to treatment. So I would guess that in some of our patients, they will feel pretty good on the 4 mg dose, but we might be considering the 8 mg/kg dose in this population of patients. But I think starting slow and building it does seem like the prudent way to go.

DR. WILLIAMS: I agree that we should start slow, but I suspect a lot of the patients

will end up on 8 mg/kg because they get a better response.

Ms. Malone, do you have another comment?

MS. MALONE: Just the whole idea that in the real world people don't just have RA. You know, they have other things going on. Some co-morbidities are a result of the RA, but also other stuff happens to their bodies. And so you can't always say well, this is a result of this RA drug. It can be the result of everything else that's going on in the body.

DR. WILLIAMS: Absolutely. That is a very good comment. Anything else you needed on this question? I think you have a sense of the Committee. Question number three is a voting question. In view of the data available for safety and efficacy, do you recommend approval of tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis?

We are using a new system of voting

at this meeting. On your microphone, there are three buttons: Yes, no, and abstain. They will light up, and you'll have approximately 20 seconds to vote yes, no, or abstain. The results will then be shown on the screen, and I will read them out.

We will then go around the table, and you will, for the record, say what you voted and have the opportunity to say why you did that.

So the question is, in view of the data available for the safety and efficacy, do you recommend approval of tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis?

Are we ready to vote? Can we turn on the machines? There you go; you have 20 seconds. Pardon? You just push yes, no, or abstain.

SPEAKER: Can you vote more than once?

DR. WILLIAMS: If you're from Florida. Okay. Have we got everybody's vote? Yes, it

keeps blinking. She will tell me when you've all voted. We have all voted, so you're going to push the magic button here. Yes 10, no 1, and abstain 0.

Ms. Malone, we'll start with you and move around.

MS. MALONE: Well, I voted yes, so I'm not the holdout. But I don't think that it's the first line of treatment, you know. I think I'd go with other biologics first, you know, because of some of the safety issues.

DR. WILLIAMS: Thank you. Dr. Felson.

DR. FELSON: I also voted yes. I think its efficacy is pretty good, and safety concerns are real, though. And I think we'll have to be monitoring this closely.

DR. WILLIAMS: Dr. Pisetsky.

DR. PISETSKY: I also voted yes. The data indicates that it's effective. There are safety concerns, and I would also wonder whether there is evidence we could assemble. There are obviously knockout mice that could help address

questions of risk for demyelination, and if there are concerns about GI. I'm also sure knockout mice could address this. So in addition, I think, to having a good follow-up data, I think we can look to other places to reassure us on safety.

DR. WILLIAMS: I'm asked to have you state your name. They really want you on record for this.

DR. PISETSKY: Oh, David Pisetsky.

DR. WILLIAMS: Dr. Hoffman.

DR. HOFFMAN: Gary Hoffman. I voted yes. And I think that the sponsor should be complimented on -- at least from my perspective in having sat in on many of these hearings over the years -- having put their drug through a more rigorous type of evaluation than any other that I've sat in on so far. I think there's been a good look at cardiovascular toxicity and other things that we had been concerned about in the past that had not been looked at as carefully or over as long a period of time.

I didn't have a chance to comment on the four versus eight, and I'll just interject that I do have once concern in that argument. And that is, this drug's not a cure, and we know that active disease begets destruction over time.

And I think we've learned from a variety of studies, especially studies and analyses that have been presented from The Netherlands, that the sooner you intervene, the more aggressively you intervene, the less damage you get. And having seen in all of these studies more efficacy in the 8 mg/kg group, albeit with slightly more concerns, I'm more inclined to lean towards the sponsor's recommendation of starting with a higher dose while we carefully monitor with post-marketing surveillance those things that we're concerned about.

But I don't see a signal here that goes beyond what we've seen with anti-TNF agents.

DR. WILLAMS: Thank you.

Dr. Blumenthal.

DR. BLUMENTHAL: David Blumenthal. I voted yes, and like with any other biologic, I think patient selection, patient education, monitoring by the prescribing physician, and monitoring by the FDA are going to be important.

DR. WILLIAMS: Thank you.

Dr. Sandborg.

DR. SANDBORG: Christy Sandborg. I also voted yes. I think that this drug does add perhaps a different wrinkle in our biologic armamentarium, and therefore may be helpful for unique subsets of patients such as TNF failures, and I think again that the key is going to be how we monitor it and design explicit post-marketing questions to be answered.

DR. WILLIAMS: Thank you. James Williams. I also voted yes. I think that the sponsors have shown efficacy, particularly in a group of patients that's difficult to treat, and that is the TNF inadequate responders. And in

addressing Gary Hoffman's concerns, I think this drug acts so rapidly that it won't be more than a couple months till you know whether you're going to go up on the does.

Dr. Turk.

DR. TURK: Dennis Turk. I voted yes. I felt that the company did a good job with demonstrating the effectiveness of the treatment, especially given the nature of the problem, the disease, and how much problem remains to be seen, the large numbers of patients who are not getting as much benefit as we'd like to see. There are safety concerns; I think we've had a lengthy discussion about the kinds of cautions that will have to be used, and I think the FDA is very good at putting those kinds of cautions out there. I think obviously we need more post-marketing data to look at some of the types of concerns that we've seen.

DR. WILLIAMS: Thank you. Dr. Stine.

DR. STINE: Robert Stine. I voted yes.

DR. WILLIAMS: Ms. Aronson.

MS. ARONSON: Diane Aronson. I voted no. While I'm really excited to hear about the efficacy presented by the patients, I really did feel like I wanted to go on record to bring up the safety concerns which I've raised already, an also the long-term information that we still don't have about the impact on the liver. That's something I didn't mention before.

I also have heard about 10 issues regarding risk mitigation that's been listed for either post-screening and/or lab tests required. And given today's medical practice, I'm just wondering what's reasonable and the amount of safety issues that can be tracked. And again, about the concomitant therapies and other diseases, I have concerns about interactions.

Thank you.

DR. WILLIAMS: Thank you.

Dr. Weisman.

DR. WEISMAN: I voted yes. I think

that the sponsor and the FDA have had a great partnership herein this drug development. Both efficacy as well as safety challenges have been demonstrated. We've gone as far as we can go to identify those challenges. And that's going to be the rub in the near future. But I think overall, risk benefit favors benefit, and that's the reason I voted yes.

DR. WILLIAMS: Thank you. There's some question whether I read out the vote totals. There were 10 yes, one no, and zero abstentions.

MS. MALONE: Could I just say one more thing?

DR. WILLIAMS: Yes. Ms. Malone.

MS. MALONE: I know that the drug company is not acting purely altruistically, but there is something to be said for patients who, even with all these so-called -- you know, I've heard them called miracle drugs, and -- and when they work for you, they are, you know. And as testimony to the two women that gave their own

anecdotal remarks. The whole idea is that nothing is perfect, and when you're putting a chemical or anything into your body, you may not always get the best results, or the same results that someone else would get.

But to have something else available, especially for those who have not benefited from this resurgence of all the interest in drugs to treat RA, and anyone who has RA, my God, and you who deal with it, see it. It's not a pretty picture. And it changes lives, and I think anything that can aid in this, even if it's imperfect, is wonderful and to be applauded.

DR. WILLIAMS: Thank you. Our last question we'll move to, and we narrowed it down by approving, or recommending approval. For immunosuppressive products approved for rheumatoid arthritis, the FDA generally expects sponsors to conduct post-marketing studies to assess safety of long-term treatment by continuing long-term treatment studies out to

five years, and to assess the effect of the product on responses to therapeutic vaccination. If you recommend approval, are there additional post-marketing studies the sponsors should conduct to further assess the safety of the products. We've actually made several recommendations already in discussing safety of things we thought out to be looked at, but this is our chance to suggest things that ought to be done other than what the company has already planned on doing and what they gave us in their pharmacovigilance presentation.

Dr. Pisetsky.

DR. PISETSKY: I think the answer is yes. One of the major issues we've talked about is cardiovascular, which in the average rheumatoid arthritis population may not be all that common, and for a reasonable size follow-up you may not see a signal even if it exists. And so one thing that I think may be worth considering is other types of studies on other aspects of vascular function that can be

done -- non-invasive studies, IMT, or something so that you're really not confined just to looking at MI and stroke, because I think there's a likelihood that there could be a cardiovascular that we're just not going to see because the data's not big enough. Because this one, I think, may be different than the other biologics because of this issue about the lipids. And therefore, I think we need to do something more than usual.

DR. WILLIAMS: But it'll take more than five years. It'll take a lot of patients, so it may take more than five years.

DR. PISETSKY: It either takes a lot of patients or looking at more things. I agree.

DR. WILLIAMS: Dr. Hoffman.

DR. HOFFMAN: I agree with Dr. Felson's concerns about LDL, although I also appreciate the fact that other surrogates going in a positive direction hopefully will also be a signal of decreased cardiovascular risk. But I think it's very important that we look at

correlates of lipid changes and cardiovascular risks over five years. From what we've learned with other drugs, I hope that there isn't a signal, but there might be a signal within five years, given a large enough denominator. So I respect David's comments in that regard, although I hope his concerns are wrong. But we'll have to study that to know. The other concern that both Davids mentioned is infection, and I think we need to not just focus on the entire user population, but particularly focus on subsets that would include the very elderly, those with chronic obstructive lung disease, and also diabetes mellitus.

DR. WILLIAMS: I like the idea that they're going to use some long-term registries to follow these patients so they can gather some of that data.

Dr. Sandborg.

DR. SANDBORG: In looking at the design for the registry in here, there's power analysis that are adequate for most everything

we're interested in, although I do note that demyelination is not on here. But for the GI perforations, there's 80 percent power in 5000 individuals over five years, but then they also did a calculation -- and again, thanks for the transparency -- if you have a 20 percent dropout, you would then not have adequate power of detecting a double increase in the GI perforations. You'd only have 52 percent as opposed to over 80 percent. So I'm wondering if one of the considerations we might want to make, if we're going to miss that very unusual rare signal, whether we should increase the size so we can pick a twofold difference?

DR. WILLIAMS: Other comments? Diane, what would you like to see done that would make you feel better about approval?

MS. ARONSON: Well, I jotted down more long-term data regarding infection, cardiovascular, and impact on the liver, yeah.

DR. WILLIAMS: Other comments on recommended studies? I personally thought that

the company really has set out a very good, vigorous program for post-marketing surveillance.

Dr. Felson?

DR. FELSON: With 5,000, does one get enough myocardial infarctions to be able to know whether that's increased? Obviously, that took a much bigger number with COS-2. And I'm looking back over the slides. I don't think we have the slide that gave you power for different events. Maybe --

DR. PISETSKY: I mean, the NSAID trials for cardiovascular -- what? Twenty, 30,000 in two years. So 5,000 is -- I don't know if 5,000 for five years is the same, but it strikes me as small.

DR. WILLIAMS: All right.

Dr. Weisman?

DR. WEISMAN: I asked Jeff what -- he obviously had been grappling with this issue internally, about cardiovascular risk -- what kinds of programs are you thinking about? It

may have to be mandated across multiple companies. It may not just be limited to one company. It may have to be multiple companies. How have your epidemiologists and colleagues recommended to you about how to assess this issue?

DR. WILLIAMS: Dr. Siegel?

DR. SIEGEL: This is a relatively new issues for biologics for RA, the issue of the cardiovascular signal. We're going to need to go back and discuss with our epidemiology colleagues what type of study would be adequate, and considerations for powering. With pediatric registries, we have begun to deal with the issue that currently our registries are product by product, and what we really need is a combined registry to get more power and have controls internally within the same registry to look at safety events.

I think that there are some registries in RA that may be helpful for getting these event rates across different

products, and we'll need to look at that more.

DR. WILLIAMS: Thank you. Further comments by the Committee? Your microphone's lit; does that mean anything, Dave?

DR. FELSON: I don't know. No.

DR. WILLIAMS: Dr. Siegel, Dr. Vesely, anything else that you want us to address? Any other issues?

DR. SIEGEL: No. I'd just like to thank the panel. This was a really useful discussion of both the efficacy and these safety issues. We appreciate that some of the safety issues are very difficult to grapple with, but we appreciate your insights from your clinical experience and your research backgrounds to help us figure out how best to deal with this.

So we thank you very much.

DR. WILLIAMS: I also want to thank the Committee. You were concise in your comments, and I think we addressed the issues, but we also quit early. The vans are here, and

so those who have tighter connections have plenty of time to get to the airport.

I thank you all.

(Whereupon, at approximately 2:26 p.m., the MEETING was adjourned.)

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