and sign outcomes that matter to patients, you see almost no difference between 4 mg/kg and 8 mg/kg. And I sort of wonder why you chose to -- I mean, I don't know that the 4 mg is any less toxic than the 8, but obviously there are toxicity concerns. I was sort of wondering why you chose to move forward without incorporating the opportunity for a 4 mg/kg dose, given that spectrum of change and improvement.

And you also commented about sort of significant effects on 50 and 70 with 8 mg/kg versus 4 mg/kg, and I wasn't sure how much of that was driven by dramatic CRP improvements. And I noticed that the 4 mg/kg every time gave you differences that were better than placebo. So I was sort of wondering why you moved to the higher and potentially more toxic dose -- whether you had other information that helped you there?

DR. WILLIAMS: Dr. Bahrt?

DR. BAHRT: I'd be glad to answer

that. Ken Bahrt, Roche. In the anti-TNF failure population, taking that first, the 8 mg/kg dose was the only dose that was consistently efficacious, especially for the ACR 50, the ACR 70, or all the other efficacy endpoints. So in that population, clearly the 8 mg/kg dose is the most effective dose.

In monotherapy, we only studied the 8 mg/kg dose, so I can't comment on what 4 would look like in a monotherapy situation. So I agree with you: In a DMARD IR population, both doses -- the 8 mg and the 4 mg dose -- were effective. And when you look at such as this slide here, they appear to be very, very similar in how they affect. If you look, however, at those patients who had an adequate response to, let's say, an ACR 20 or an ACR 50 when they were on the 4 mg dose in the clinical trial, when they went to the escape part of the clinical trial, where all the patients then increased to 8 mg/kg, these patients had an increase in

their response, even though they were doing well on the 4 mg/kg dose.

So looking at that, showing that even patients who responded well to the 4 had enhancement of that response when they went to the 8 mg/kg dose, and the majority of the patients who were on the 8 mg/kg dose did do statistically better than the 4 mg/kg dose in the DMARD IR population.

Slide up, please. If you can see, these are patients from the 822 trial who were having an ACR 50 response at the end of the clinical trial, and then when they went to open-label tocilizumab at 8 mg/kg, they had an enhancement of that response. More of the patients achieved the ACR 50 endpoint. So while I agree with you that both doses are effective, and both doses should be considered based upon the individual benefit risk for that patient, our position is that the 8 mg/kg dose is the more effective dose for the majority of patients.

DR. FELSON: Let me just remind you also that you made a reasonably persuasive case that efficacy continues to grow over time.

DR. BAHRT: Correct.

DR. FELSON: You don't have a control group here. Why don't you just interpret that as the continued use of an effective dose of tocilizumab with gradually increasing efficacy over time, rather than a sudden switch to a more -- I mean, I don't necessarily disagree with you, but I'm not sure we'll ever know whether it's the 8 mg/kg dose or the 4 mg/kg dose. Some of that increased efficacy could just be a dramatic CRP that occurs, and no clinical improvement that a clinician or a patient would remark on, I guess.

Let me switch, because I wanted to ask you about monotherapy and development of immunity to the compound for a minute. There were some anaphylactic reactions and some infusion reactions, and I wanted to know, number one, whether those tended to occur in

people on monotherapy as opposed to people who might be getting another disease-modifying drug that might prevent the development of immunity to those treatments.

And I wondered if you had looked at the development of immunity to your treatment in monotherapy versus people who'd had DMARDs that might prevent that autoimmunity from developing. Can you comment on that?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Sure. Dr. Krasnow, Roche. We look at two different things. One is the clinical events of infusion reactions. And what we do note is, if we look at the fact that there were three infusion reactions on the 4 and the 8 mg, we also note that as far as anti-tocilizumab antibodies, it does occur more often in patients who are not on a concomitant disease-modifying agent such as methotrexate.

And this is, I think, well-acknowledged. The point that I'd like to make, however, is that both for efficacy

and for safety, it is really the clinical impact of those antibodies. And when we look at the clinical impact of those antibodies, we find the following. Can you please put the slide up.

It's that a total of 1.8 percent of patients developed antibodies to tocilizumab, and of these, 12 patients experienced an infusion-related reaction and were also positive for anti-TCZ antibodies. And this includes the broad host of terms for infusion reactions, including hypertension, headache, et cetera -- a broad spectrum.

And five of these patients experienced a serious event leading to withdrawal. One percent of patients developed neutralizing antibodies, meaning that they block the binding of tocilizumab to the soluble Interleukin-6 receptor. And neutralizing antibody-positive patients had a similar safety profile to patients who did not develop anti-tocilizumab antibodies.

And there was no association between neutralizing antibody development and loss of clinical response. And only one of 38 patients discontinued due to lack of efficacy in association with these antibodies.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: My question relates to the monitoring of white blood counts during the course of therapy. What is the time that these should be monitored with respect to the various infusions? Since neutrophils are very rapidly turning over (inaudible), they could really have major changes over time.

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Yes. Dr. Krasnow, Roche. Our current recommendation for routing monitoring would be to monitor the neutrophils toward the end of the dosing interval. Now, obviously, if someone is at risk for infection, the other thing about monitoring neutrophils is, one has to really reset the baseline, because

the neutrophil count will be reduced by approximately one to 2000, depending on the patient, and so if you're looking for neutrophil counts as an indicator of early infection, then you would monitor it as clinically needed. But because of the fact that the neutrophil count does decrease and then slowly returns up to baseline, if you have a value shortly after administration, then you would be treating the lab value without any necessary clinical consequence. So what we're looking for is to really get a determination around the end of the dosing interval.

DR. PISETSKY: My understanding of the rationale for monitoring would be to prevent serious neutropenias. Wouldn't you therefore want to know what the white count is at the lowest point, rather than at the highest point?

DR. KRASNOW: You could. Let me put in more detail what occurs during the dosing interval to illustrate this. Slide up, please. This is a study in healthy volunteers, and what

we see here is the different doses. In red is the 2 mg, followed by the other increasing doses. And what we see here at time zero, this is the time of administration of tocilizumab. And as we can see on this slide, the doses administered are in many cases greater than that which we would do clinically. And if we then look at the 2 mg dose, what we see is that the nadir is similar for all of the groups, but then what we see is that the rise is very rapid for the 2 mg, and then would be intermediate for the 4 mg, and then the 8 mg. And as we can see, it is slowest as far as its recovery with the highest doses.

So what we see is that a similar trough -- so if you wanted to know the absolute trough, then you would monitor shortly after administration, and if you want to know -- and what we have done in our clinical trials is, we have monitored at four-week intervals, and understand what the clinical relationship is for those patients

at about the time of the trough levels of tocilizumab. So it would be at your discretion as to when you felt it would be most appropriate to monitor your individual patient.

DR. WILLIAMS: Dr. Sandborg?

DR. SANDBORG: I have a question about the pharmacovigilance plans, specifically the registry for the U.S. The question is, how will that differ from the long-term extension, and clarify that there will be 5000 patients exposed to medication in that registry.

DR. WILLIAMS: Dr. Van der Auwera?

DR. VAN DER AUWERA: Philippe Van der Auwera, Roche. Can I have the slide on the sample size calculation? Slide up, please. You can see here various calculations of ability to detect risk ratio depending on sample size. What I propose as a target is indeed 5,000 patients, 25,000 patient years, so each patient would be there for five years. We'd have the ability to detect with the power of 80 percent a

risk ratio of about 1.4 for the cardiovascular events. And if you are interested in GI perforation, this would be around 2. The exact sample size will have to be determined later on, when we are going to discuss with the agency, to have exactly what is the kind of risk ratio that we would like to be able to measure with certainty.

DR. SANDBORG: So just to clarify, this will be in addition to the long-term extension?

DR. VAN DER AUWERA: Yeah, indeed, because the ability of the registry is to be able to compare with patients who are being treated with DMARD or DMARD plus other biologics, certain biologics. That's where we would be able to compare what is the additional risk that perhaps tocilizumab is conferring to this population during treatment.

DR. WILLIAMS: Ms. Aronson?

MS. ARONSON: I have a question about the corticosteroid use in the study. In the

monotherapy study, I wonder if you have any information on the breakout of the patients on corticosteroids. I note that about 48 to 69 percent of all patients in all the studies were on corticosteroids. And then in studies 822, 23, and 63, only 29 percent in the placebo were on corticosteroids, versus 51 and 52 in the 4 mg and 8 mg. And I also noted that there were more deaths in the 8 mg versus the 4 mg with DMARD, and I wondered if there was an impact or some mitigation going on?

DR. WILLIAMS: Could you identify yourself?

MS. DAVIS: Clare Davis from Roche. In all our clinical trials, the patients are to remain on a stable dose of corticosteroids for the six-month period at a maximum dose of 10 mg per day.

The majority of patients across all the trials, approximately 60 percent, were on corticosteroids at baseline, and the mean daily dose is around 7 mg.

I'll hand you over to Dr. Krasnow.

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Dr. Krasnow for Roche. I'd like to address your question regarding the deaths.

There were no deaths in the 4 mg/kg treatment arm, whereas in the 8 mg/kg treatment arm, there were deaths both in the monotherapy and the combination therapy. We don't have an explanation based on corticosteroid use for that observation.

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: I'd like a follow-up of Dr. Pisetsky's question about the monitoring of the white count. Do you recommend that we should monitor the white count before each infusion, for safety purposes, like we used to do with gold therapy, for instance, because you never knew when the white count or platelet count was going to drop, but you wanted to know it before you instituted the next dose. Is that the recommendation that you're making?

DR. WILLIAMS: You're dating yourself with the reference to gold, Mike.

DR. WEISMAN: Only you would know that, though, Jim.

DR. KRASNOW: That is not the recommendation that we are making. What we see is, with the white count, with the platelets, and with all the hematologic parameters, what happens is, you get a fairly rapid drop. And then if we look at four and eight-week intervals, it's relatively stable. There's obviously some variation, but we don't get a situation whereby at one monthly interval it's at 1000, and the next one is at 4000, and then below, or not very often. And so what we've done is, we've gone to a monitoring frequency of every three months in our extension studies, and the patients have done very well with that monitoring frequency.

Does that address your question?

DR. WEISMAN: Yes.

DR. WILLIAMS: Dr. Hoffman?

DR. HOFFMAN: I previously asked about the effect of co-morbidities on skewing of adverse events. I meant to also include in that the effect of age, and you cautioned us that you only had 48 patients in the aggregate, from all of these patients in the studies, that were greater than 75 years old.

And when we looked at the data on slide 34, we saw that there was a trend towards efficacy, but that did not reach statistical significance. So along those lines, I'd be interested in knowing whether or not there was a least a trend towards increased infections and other adverse events in those people over the age of 75, as would be logically expected; whether, because of the limited data on that very elderly group, there would be a caution in your intentions as far as labeling about the use of this agent, should it be approved, in patients over the age of 75?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Yes. First of all I'd like to state that we do, as you said, have a limited exposure in the group over 75, but we do have a larger exposure in the group over 65, and it's the group over 65 that may be more informative.

So with respect to serious infections -- thank you; slide up, please -- with respect to serious infections, if we look at the bottom part of this slide, what we note for the age groups of 50 to 64 and 65, and if we look, we can look at the difference in infections. And the difference in infections does increase with age.

And this was also seen in the placebo arm, as we see on the far right-hand side over here as well. And it's a general, I think recognized, phenomenon that increases in infection occur with age. The real question is, is there an effective mitigation by going from 8 mg to 4 mg in order to decrease the risk of infection?

And from the data that we have to date -- this is for serious infection; these are patients that are at higher risk -- but going from 8 to 4 does not mitigate the risk, from the data we have to date.

DR. WILLIAMS: Dr. Blumenthal?

DR. BLUMENTHAL: I have two questions. The first relates to slide P131, risk mitigation for the liver. It's implied but not explicitly stated here that patients should be screened for hepatitis B surface antigen and hepatitis C viral replication, and if they are found to have these things, they should not get this drug. Is that the company's stance on this?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Yes, Dr. Krasnow, Roche. The company's position is that we have very limited experience with patients who have hepatitis. We have a small number of patients who have been dosed primarily in Japan and have really not had any incident with the drug. But because of our paucity of information, we are

not in a position to attest to the safety of tocilizumab in patients with chronic hepatitis infection.

DR. WILLIAMS: Dr. Fletcher?

DR. FLETCHER: Yes, I was wondering, to follow up to Dr. Felson's question about immunogenicity, could you briefly describe the sensitivity of your assay, both the anti-drug antibody and neutralizing assay, for the presence of the drug? And a corollary of that: When you actually were able to sample for anti-drug antibodies, particularly in those who had infusions relative to that, because some assays there is interference with the drug being present, so sometimes you can underestimate the presence of anti-drug antibodies and/or anti-neutralizing antibodies.

MR. WINTER: Michael Winter, safety in Basel. We have used three different assay types for the measurement or identification of anti-tocilizumab antibodies. The one, the screening assay, is an assay where tocilizumab

is immobilized on the plate, and deoxygenize it, tocilizumab is used for identification of antibodies of the IgG, or independent of their either type from, so in this situation, an antibody would cross-link to immobilize with the fluid-phase tocilizumab and can be identified by the detection system of the peroxidase label and the deoxygenate antibody.

The assay has shown sufficient sensitivity, such as shown by this white paper from Meyers Ruiz (?), and of course because antibodies which are -- the presence of tocilizumab per se does of course interfere with the sensitivity of the assay system, because the requirement of the assay type is cross-linking of the immobilized with the fluid phase. And under high exposure of tocilizumab, we see depletion or a clenching of the signal.

Now, that has been reflected in the sampling strategies, so we use pre-dose samples at trough levels to screen for the

presence of neutralizing antibodies.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: Let's get to the question about the efficacy. You're reporting DAS28s of 3.2, of 40, 50 percent, and DAS 2.6 of 30 percent, which is remission, just about. Yet you're starting with a population that has a very high joint count; you know, 30 or so. Can you explain which population is showing this remission? Is it -- are you having people who drop from 30 tender and swollen joints down to two or three, or is this somehow a reflection of a fairly dramatic effect on the CRP or ESR which gets reflected in the DAS?

DR. WILLIAMS: Dr. Bahrt?

DR. BAHRT: Ken Bahrt, Roche. I don't have an exact answer to your question, but I can tell you that if we look the patients who did achieve a DAS28-defined remission of less than 2.6, what you can see is that over approximately half of these patients on the 8 mg dose achieve a greater than 70 percent improvement in their

tender and swollen joints. Those patients who have less than a 70 percent improvement in their tender and swollen joints are relatively low. So I think it's a broad sample of all the patients that are responding to the tocilizumab to get into the remission state, not one particular subset that we've identified.

DR. WILLIAMS: Ms. Malone?

MS. MALONE: Yes, going back to slide 138, Dr. Van der Auwera. When you talk about patient, nurse, and physician education, just what do you mean by that? How are they going to be educated, other than -- you know, the old idea was that the drug rep would come in and do a little seminar. What I'm finding is, nurses have been complaining that because they're the ones doing the entry -- or they're not really complaining, but remarking -- because they're the ones who are spending the most time -- with our health care system the way that it is -- they're spending the most time with the patient.

And the patients are hungry for information about these drugs, other than what rheumatologists, as good as they are and the time that they do give -- they need more time. And my concern is that it's just not going to be in a TV-scripted message.

DR. WILLIAMS: Dr. Van der Auwera?

DR. VAN DER AUWERA: Philippe Van der Auwera from Roche. Thank you very much for these questions. These are absolutely great questions.

The nurses are indeed key, because they are going to see the patients most of the time. So we are going to develop tools that are going to allow nurses to explain to patients, especially at the beginning of the therapy, to reinforce what is important for them -- first, to understand about the product, but more importantly, what are the signs and symptoms that they have to report. And there will be specific questions elicited from the nurse whenever the patient is coming

from next infusion.

We are going to do that with flip-chart material. We are going to produce material as well like video material. But what is more important is really the contact between the nurse and the patients. Likewise, at the level of the health care professionals, there will be CME sessions to make sure that there is independent education and information of the prescribers about the characteristics of this product, the need to alert the patients on signs and symptoms that they have to report, including to their GP.

DR. WILLIAMS: The final question by Dr. Felson.

DR. FELSON: A couple of short ones. One is, the patients who developed both upper and lower GI perforations, were they on other medications that cause this, like nonsteroidals, as co-therapy, or even steroids? Do you have any data on that?

DR. LEFF: In terms of the lower GI

perforations, extending all the way through our reporting period there were 14 of these cases, including Chugai. And on the right you can see 10 out of those 14 were on steroids. Nine out of 14 were on NSAIDs, both of which are recognized risk factors for lower GI perforations. And for upper GI perforations, there were six total. Five of those six were on corticosteroids, and all six were on NSAIDs.

DR. FELSON: Another -- so I asked earlier about the development of antibodies to this compound, and wanted to know, I think, specifically -- and maybe you answered this, but help me if you didn't -- did you see a different rate in those on monotherapy than those on combined DMARD and tocilizumab therapy?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: A higher rate of what adverse event? Can you please specify?

DR. FELSON: I think either the anaphylaxis injection reaction-type events, or the immune reaction and development of

antibodies to tocilizumab. Was that somehow prevented by or lessened by the co-use of disease-modifying drugs, like has been seen in other biologics?

DR. KRASNOW: Yes, it is lessened by the concomitant use of methotrexate or other DMARDs.

DR. FELSON: Do you have data to support that statement?

DR. KRASNOW: We can provide the instances to you. I have data related to the infusion reaction specifically. I can access that and provide it to you at the break; I don't have it immediately.

DR. FELSON: So if that were the case, then why would you recommend monotherapy as a treatment option? Why wouldn't you, like with some other biologics, recommend co-use with disease-modifying drugs to prevent that from occurring?

DR. KRASNOW: If we look in the monotherapy, what we have is, we had one

hypersensitivity reaction. And so, based on one hypersensitivity reaction, we feel that the benefit-to-risk ratio is highly favorable for patients. And we are recommending that if patients are appropriate to receive tocilizumab with or without a DMARD, that this not be a rate-limiting step due to the incidence of this clinical event.

DR. WILLIAMS: Thank you to the sponsor.

We will now take a 10-minute break, and we will return here at 10:54.

(Recess)

DR. WILLIAMS: We will now turn the time over to the FDA for their presentation. It will be done by Sarah Okada from the FDA.

DR. OKADA: Good morning. In these next minutes, I'll be presenting a brief background on RA clinical development programs and claims, followed by an overview of the tocilizumab RA pivotal trials, which will include a very brief reminder of the key

efficacy results, and then a more extensive look at the safety results in these trials.

In the early phases of drug development for RA, trials commonly include an initial study of safety of the investigational treatment in combination with methotrexate and a proof-of-concept study utilizing the ACR 20. During Phase 3, larger randomized control trials of at least three months' duration are expected that can characterize the treatment effect of the investigational treatment as monotherapy and in combination with other DMARDs, especially methotrexate.

Trials may include clinical practice-type trials, which assess the safety of add-on therapy with prevalent DMARD regimens. Historically, after the product has been approved, sponsors have submitted studies to support expansion of the initial indication to include early RA and to support use of the product as first-line treatment.

Other post-approval studies have also include studies in juvenile idiopathic arthritis and comparative studies. Long-term -- for example, five-year -- safety studies and studies of the impact of treatment on immunization response have also been required as post-marketing commitments.

As per the currently published RA guidance document, FDA has recognized a discrete set of claims in RA. These include the foundational claim of reduction of signs and symptoms, demonstrated by the proportion of ACR 20 responders at three months or longer. Additional claims include inhibition of structural damage demonstrated by a change from baseline and radiographic scores at the end of a controlled period of at least six months, with a total duration of radiographic follow-up to at least one year.

Improvement in physical function may be demonstrated by the proportion of patients achieving clinically meaningful

improvement; for example, greater than 0.22 units decrease in the health assessment questionnaire disability index score at the end of a controlled period of three months or longer, with evidence that this improvement is maintained for an extended period of time.

A claim of major clinical response may be granted for demonstration of a higher proportion of patients achieving ACR 70 and maintaining this improvement for six months or longer. Finally, a claim of complete clinical response or remission may be granted for a demonstration of a higher proportion of patients achieving remission by ACR criteria, along with radiographic arrest, for six months or longer, while on therapy or off therapy, respectively.

The data in the tocilizumab biologics license application is intended to support an initial claim of reducing signs and symptoms of moderately to severely active RA, and is comprised of 24-week data from

five pivotal studies. These studies covered the range of RA patients from early RA to more refractory patients, and includes data for tocilizumab monotherapy, tocilizumab given with concomitant methotrexate, and tocilizumab given with other non-biologic DMARDs. Patients completing the core randomized controlled studies were allowed to enroll into long-term extension studies upon completion, for a total of five years. For this BLA, interim data has been submitted. As of the date of cutoff for the application, close to 1,500 patients have received tocilizumab for up to 18 months.

Because the sponsor has already presented the efficacy data in detail, and there are no major issues that we have with the efficacy data in the submission, I will only very briefly recapitulate the primary efficacy findings in the next four slides.

Our analysis of the efficacy data in the submission is consistent with the

sponsor's. We concur that in all studies, treatment with tocilizumab resulted in a higher proportion of ACR 20 responders at week 24 compared to controls, and that this difference was statistically significant.

The primary endpoint was further explored in subgroup analysis by demographic characteristics and geographic region. These analyses demonstrated that treatment with tocilizumab resulted in a higher proportion of ACR 20 responders than did treatment with placebo for all subgroups analyzed.

Similarly, for subgroups by disease characteristics, treatment with tocilizumab resulted in a higher proportion of ACR 20 responders than did treatment with placebo, for all subgroups analyzed.

Sensitivity analyses, utilizing different imputation techniques for missing data, such as last observation carried forward and baseline observation carried forward, were performed. The results of

these analyses were consistent with the primary analysis results.

Now I'll be proceeding to a more extensive look at the safety profile of tocilizumab.

This submission contained 24-week safety data from the five pivotal trials, including six-month interim data from study 17823, which is designed as a two-year study. These studies were of sufficiently similar design to allow for pooled analyses of the six-month controlled data by treatment groups. Long-term safety information from RA patients treated with open-label tocilizumab at 8 mg/kg was also provided in the BLA. These data are derived from two open-label extension studies which are ongoing.

Almost 3,800 patients have been exposed to tocilizumab in the Roche RA program, and almost 1500 patients have been exposed to tocilizumab for up to 18 months. The majority of tocilizumab exposure has been

to the higher dose of 8 mg/kg.

The majority of patients in the tocilizumab RA pivotal trials experienced at least one adverse event during the course of the trial. The proportion of patients experiencing an adverse event in the tocilizumab treatment arms was similar to the proportion of patients experiencing an adverse event with methotrexate monotherapy and was higher than with placebo. The proportion of patients experiencing an adverse events in the long-term extension was higher, as might be expected, given the longer duration of observation.

Deaths were uncommon, but were observed in all treatment arms during the six-month controlled period, except in the tocilizumab 4 mg/kg treatment arm. The highest proportion of deaths, three out of 288 patients, or 1 percent, occurred in the tocilizumab 8 mg/kg monotherapy arm of study 17824.

The incidence of serious adverse events was similar in the tocilizumab groups, at 6 percent, compared with placebo at 5 percent. Tocilizumab and methotrexate monotherapy groups had fewer adverse events, at 4 percent and 3 percent, respectively. Again, the proportion of patients experiencing a serious adverse event was higher in the long-term extension. I'll discuss exposure-adjusted incidence of death and serious adverse events in further detail in a moment.

The proportion of patients experiencing an adverse event leading to withdrawal was small, less than 5 percent in each treatment group, but was lowest with placebo. During the double-blind controlled portion of the studies, dose modification entailed temporary withholding of the scheduled dose; for example, for the first occurrence of AST or ALT elevation greater than three times the upper limit of normal,

or for non-serious infections. Background DMARD therapy doses could be modified for toxicity, and study 17824 specified scenarios for methotrexate modification in the protocol. Dose reduction from tocilizumab 8 mg/kg to 4 mg/kg was allowed in the long-term extensions for a wider range of safety reasons and was accordingly higher.

In the placebo-controlled portion of the trials, patients could escape at week 16 if they had inadequate response. In general, a higher proportion of patients in the placebo treatment groups entered escape. Thus, the overall exposure time of patients to placebo was shorter than the designated six months. Conversely, the majority of patients in the long-term safety population have been exposed to tocilizumab treatment for at least one year.

To account for these differences in exposure for comparison by treatment arm, exposure-adjusted incidence rates were

calculated for deaths, serious adverse events, serious infectious events, and malignancies, summarized here.

Overall, the exposure-adjusted incidence rates of death were not elevated in the tocilizumab treatment groups compared to the control group, with the exception of the tocilizumab 8 mg/kg monotherapy treatment group. This finding is difficult to interpret because of the small number of deaths involved and the lack of similar increase in the tocilizumab 8 mg/kg plus DMARD group in the other studies. The incidence of death in the long-term extension did not rise.

The observed exposure-adjusted incidence rate of 2.4 deaths per 100 patient years in the tocilizumab monotherapy group is similar to expected rates in the RA patient population based on published mortality rates. For example, in the Olmstead County RA cohort, death rates for female and male RA

patients were 2.4 to 2.5 deaths per 100 patient years, respectively.

The exposure-adjusted incidence of malignancies, including non-melanoma skin cancers, was similar in all treatment groups, including placebo, at 1.5 to 1.6 malignancies per 100 patient years, with the exception of a slightly higher rate of 2.4 malignancies per 100 patient years observed in the methotrexate monotherapy group. Again, incidence did not rise in the long-term extension. Published background rates in RA patients range from 1.3 to 1.4 malignancies per 100 patient years, as in the Danish Cancer Registry and the British Biologics Registry. Therefore, the observed rate in the studies was slightly higher, but is in the general vicinity.

A similar incidence of serious adverse events was noted in the tocilizumab treatment groups compared to placebo. Tocilizumab and methotrexate monotherapy

groups had the lowest exposure-adjusted incidence at 10 and 12 events per 100 patient years, respectively. The rate of serious adverse events did not increase with increasing duration of tocilizumab exposure observed in the long-term safety population.

The incidence rate of serious infections was highest in the tocilizumab 8 mg/kg plus DMARD combination treatment group, at 5.7 serious infections per 100 patient years, and was slightly lower in the 4 mg/kg plus DMARD group, at 4.7 serious infections per 100 patient years. Both rates exceeded the observed rate of 3.9 events per 100 patient years in the placebo plus DMARD group. Tocilizumab and methotrexate monotherapy groups again had the lowest exposure-adjusted incidence, with 3.2 and 1.6 serious infections per 100 patient years, respectively.

The rate of serious infections again did not increase in the long-term

extension. Rates of serious infections in RA patients taking TNF inhibitors have been published as approximating five to six serious infectious events per 100 patient years, compared to two to four serious infections per 100 patient years in RA patients taking non-biologic DMARDs.

During the tocilizumab RA pivotal studies and long-term extensions through the data cutoff of October 1st, 2007, five patients died of cardiac etiologies, to include four myocardial infarctions and one cardiac failure, and four patients died of infectious etiologies while on tocilizumab treatment. Overall, the numbers and causes of death in the program appear to be consistent with what might be expected for the underlying patient population.

As discussed, the overall exposure-adjusted incidence of malignancy in the tocilizumab RA studies appears to be close to what might be expected in the RA

patient population. Few malignancies were observed during the six-month controlled period of the RA pivotal studies. During the long-term extensions, a total of 65 neoplasms or malignancies were diagnosed. Lung neoplasms and cancers occurred most commonly, followed by basal cell skin carcinomas. The relative risk of lymphoma is considered to be higher in RA patients; however, thus far only a single case of lymphoma has occurred with tocilizumab treatment in the Roche RA program.

Overall, the pattern and frequency of malignancies observed in the tocilizumab RA program to date appears to be consistent with what might be expected in RA patients and does not clearly implicate an additional risk attributable to tocilizumab treatment.

Tocilizumab treatment was associated with a higher risk of serious infections. Of these, pneumonia and cellulitis were by far the most commonly

occurring serious infections. In addition to commonly occurring bacterial infections, treatment with tocilizumab was associated with an increased incidence of herpes zoster, including herpes zoster ophthalmicus. No other viral reactivation events were noted; however, a single case of serious Epstein-Barr virus reactivation complicated by non-Hodgkin's lymphoma and resulting in death, was observed in the Chugai RA trial.

Patients with a history of recurrent infections, including hepatitis B, hepatitis C, and herpes zoster, were excluded from the Roche RA trials. Patients were also excluded from the studies if they had a history of or known active mycobacterial infection, but were not specifically required to have TB screening or prophylaxis. In fact, 68 patients, 52 in the tocilizumab treatment groups, had a history of TB or a positive PPD prior to study start.

Despite this and the global nature

of the studies, only two cases of TB have been diagnosed in the program thus far, one case of staph and TB-infective arthritis, and one case of urinary tract infection. No cases of reactivation TB have yet been diagnosed.

Two opportunistic infections were diagnosed: One case of pneumocystis pneumonia and one case of mycobacterium avium intracellulare pneumonia. Thus far, the overall safety profile of tocilizumab with respect to infections is consistent with that of other immunosuppressants and implicates an increased risk of serious infection with tocilizumab treatment.

As discussed exposure-adjusted rates of serious adverse events were similar for placebo and tocilizumab in combination with DMARDs, at 16 and 16 per 100 patient years, respectively. Serious adverse events were lower for the tocilizumab and methotrexate monotherapy groups, at 10 and 12

per 100 patient years, respectively. And rates did not rise in the long-term extension. Serious infections were the most common type of serious adverse events, with 2 percent incidence in the controlled period and 5 percent in the long-term extension. Gastrointestinal disorders and injuries to system organ classes were the next most common. The injury system organ class was primarily populated by events of falls and fractures. GI events included GI perforations, which I will discus in greater detail in a moment.

As of the final data cutoff for the safety update for the BLA, 15 MI were diagnosed in approximately 4,100 patient years' exposure, for a rate of .35 per 100 patient years. This rate is not elevated compared to published rates of MI in RA patients, which range from .47 per 100 patient years in the ARAMIS database to .76 per 100 patient years in the National

Data Bank for Rheumatic Diseases.

Similarly, the rate of stroke events in patients treated with tocilizumab during the Phase III studies is not elevated compared to published rates. Nine CVA were diagnosed in the same period, for a rate of .22 per 100 patient years. Published rates range from .11 per 100 patient years in female RA patients within the Nurses' Health Study to .76 per 100 patient years in the U.K. General Practice Research Database.

This truncated table summarizes the most common adverse events causing discontinuation. The study protocols mandated discontinuation for patients meeting certain laboratory criteria, such as persistent or recurrent AST or ALT above three times the upper limit of normal, isolated AST or ALT values greater than five times the upper limit of normal, and elevated total bilirubin above 2.5 mg/dL, as well as absolute neutrophil counts below 500. As

summarized here, these protocol-mandated laboratory discontinuations were the most common reason for discontinuation. Laboratory abnormalities will be discussed in further detail later. Infections and malignancies were the next most common types of events causing discontinuation.

In the global RA tocilizumab program, to include the Roche and Chugai studies as of December 31, 2007, approximately 4,700 patients were exposed to tocilizumab for approximately 8,000 patient years of cumulative exposure. In this time period, a total of 16 GI perforation events occurred in 15 patients. The duration of tocilizumab exposure before event occurrence varied from 1 to 36.

Based on exposure-adjusted incidence rates and compared to RA patients in the United Health Care Database and the MarketScan Database, RA patients in the tocilizumab global program had a slightly

higher incidence of upper GI perforation events and a similar incidence of lower GI perforation events. During the controlled period of the Roche RA pivotal studies, a total of three GI perforation events occurred in the tocilizumab 8 mg/kg treatment group, compared to none observed in the control groups or the 4 mg/kg treatment group.

Four patients have experienced in the same time period a demyelinating neurologic event. Utilizing the exposure just mentioned, the incidence rate of these events is .05 per 100 patient years. The background rate of demyelinating disorders in RA patients is not currently known.

Treatment with tocilizumab appeared to result in dose-related changes in certain hematology parameters. Overall, decreases in neutrophil counts and platelets were small, and counts remained within the normal range, reverting back to baseline once treatment ended at week 24. Few patients reached the

protocol-mandated discontinuation point of an absolute neutrophil count less than 500 during the six-month controlled period. However, those who did were on tocilizumab treatment. Discontinuation criteria were not pre-specified for other hematology parameters. A higher proportion of tocilizumab- treated patients met protocol-defined criteria for markedly low white blood cell count or neutrophils.

However, these low white blood cell counts were not typically associated with infectious adverse events.

Results were similar for the long-term extension. Although very low overall, a higher proportion of tocilizumab-treated patients met protocol-defined criteria for at least one markedly low platelet count, but few of these patients had replicated values meeting these criteria. Low platelet counts were not typically associated with bleeding adverse

events.

No patients were discontinued or required dose modification or interruption for lipid parameter abnormalities during the controlled period. Lipid-lowering agents could be initiated at the discretion of the patients' health care providers, but were not mandated in the study protocols. The proportion of patients started on lipid-lowering agents in RA pivotal trials and extensions does not appear to be excessive at approximately 1 to 2 percent in the controlled period and 7 percent in the long-term extensions.

As previously discussed, MI and stroke rates in the RA pivotal trials were not elevated compared to rates described in the literature. Very few patients experienced markedly low HDLs. However, a higher proportion of patients in the tocilizumab treatment groups met sponsor-defined criteria for markedly

abnormal elevations in total cholesterol, LDL, and triglycerides. Treatment with tocilizumab appeared to result in dose-related changes in lipid parameters. Overall, mean changes were incrementally small; however, all lipid parameters, including total cholesterol, HDL, LDL, and triglycerides, were increased. The ratio of total cholesterol to HDL was also increased.

Treatment with tocilizumab appeared to result in dose-related changes in certain hepatobiliary parameters and was overall associated with small increases in liver enzyme tests and bilirubin. Per protocol, patients were discontinued from the core studies if they experience two transaminase elevations greater than three times the upper limit of normal on treatment, any transaminase elevations greater than five times the upper limit of normal, any total bilirubin greater than 2.5 mg/dL, and any unconjugated bilirubin levels greater than

two times the upper limit of normal.

The number of patients actually discontinued for these reasons was low, but the proportion was higher in the tocilizumab treatment groups. Dose modification or interruption for hepatobiliary laboratory abnormalities was also more frequent in the tocilizumab treatment groups compared with placebo, although it was also increased with methotrexate.

Overall, tocilizumab treatment was associated with a higher incidence of protocol-defined markedly abnormal AST and ALT elevation. The highest incidence, particularly of ALT elevation, was observed in the tocilizumab 8 mg/kg plus DMARD group of the controlled period and in the long-term extension studies. The incidence in the 4 mg/kg plus methotrexate and methotrexate monotherapy groups was slightly lower, but still elevated compared to the placebo control group. The incidence was yet lower

in the tocilizumab 8 mg/kg monotherapy group, but was also still elevated compared to placebo.

This table summarizes the hepatobiliary worst values in the tocilizumab studies by treatment group. In the categories below the red line, you can see that a small percentage of patients experienced elevations in AST or ALT above three times the upper limit of normal, or had an abnormal total bilirubin. A higher proportion of patients experienced AST and ALT abnormalities in the tocilizumab combination therapy groups across the range from mild to more significant abnormalities.

A higher percentage of patients in these two groups also experienced elevations in total bilirubin. However, no instances of liver enzyme elevation greater than three times the upper limit of normal with concomitant increase in total bilirubin to greater than two times the upper limit of

normal were noted in the six-month safety population.

I will describe a single case of Hy's law criteria and describe the criteria in detail in a moment. The pattern of liver enzyme elevations was very similar in the methotrexate and tocilizumab monotherapy treatment arms of study 17824, where both monotherapy arms showed fewer instances of liver enzyme elevation compared to the combination treatment groups.

However, tocilizumab monotherapy was associated with a higher rate of total bilirubin elevation up to three times the upper limit of normal. Overall, in patients experiencing liver enzyme elevations who continued on study, modification of treatment regimen led to a decrease or normalization without subsequent elevation of liver enzymes or occurrence of hepatobiliary adverse events.

These modifications could include a

reduction of the dose of DMARD, an interruption of tocilizumab dosing, and/or reduction of tocilizumab dose from 8 mg to 4 mg/kg. Currently available data on over 3700 patients treated with tocilizumab for up to two years contain no clinical events of hepatitis or hepatic failure.

I want to step back a moment and discuss the issue of predicting serious hepatotoxicity, and particularly Hy's law, in further detail. Hy's law is based on the observation by the eponymous Dr. Hy Zimmerman that drug-induced jaundice caused by hepatocellular injury and without an obstructive component has a high rate of bad outcomes, approximately 10 to 50 percent mortality in the era before liver transplants.

The components of Hy's law are a combination of transaminase elevation to greater than three times the upper limit of normal and total bilirubin elevation greater

than two times the upper limit of normal, without evidence of biliary obstruction such as elevated alkaline phosphatase or Gilbert's syndrome. Based on original estimates of mortality, severe drug-induced liver injury can be estimated to occur at a rate of at least one-tenth the rate of Hy's law cases. Hy's law has been utilized by the FDA to identify drugs likely to be capable of causing severe liver injury.

A single Hy's law case was identified in the tocilizumab global RA program, and occurred in the long-term extension of the Roche RA studies submitted in this application. The patient is a female in her late fifties who completed six months of tocilizumab 8 mg/kg therapy with only isolated increases in total bilirubin to greater than one times the upper limit of normal, and without simultaneous increase in transaminases or alkaline phosphatase.

She enrolled in the long-term

extension and began methotrexate at 20 mg weekly, without dose titration, in addition to open-label tocilizumab at 8 mg/kg. At week five of the long-term extension, the patient was noted to have elevated AST to two times the upper limit of normal, elevated ALT to four times the upper limit of normal, and elevated total bilirubin to less than two times the upper limit of normal.

Two doses of methotrexate and one dose of tocilizumab were skipped, but by week nine the patients AST peaked at greater than 10 times the upper limit of normal, her ALT at greater than 16 times the upper limit of normal, and her total bilirubin at greater than two times the upper limit of normal. Tocilizumab and methotrexate were withheld, and the elevations ultimately normalized by week 12.

However, at week 11, methotrexate was restarted at 10 mg per week, and with normalized enzymes, the patient was restarted

on tocilizumab 4 mg/kg at week 12. By week 15, the patient's transaminases and bilirubin were again above the upper limit of normal, and the patient was discontinued from study treatment and withdrawn from the study. These abnormalities resolved by week 20.

The patient did not have clinical adverse events associated with these laboratory abnormalities.

This case was confounded by the concomitant initiation of relatively high-dose methotrexate, which has known hepatotoxicity, but also demonstrated positive re-challenge to tocilizumab. Using the estimate of severe drug- induced injury as occurring at one-tenth the rate of Hy's law cases, a single case in approximately 4,700 patients in the tocilizumab global RA program could portend one case of severe liver injury in 47,000 treated patients.

Although the mechanism of action of liver enzyme abnormalities with tocilizumab

has not been ascertained, there are plausible mechanisms by which hepatocellular injury could occur with anti-IL-6 receptor treatment.

First, IL-6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore, inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults. Also, hepatocytes express high levels of IL-6 receptor.

Therefore, with ubiquitous anti-IL-6 receptor monoclonal antibody binding in the liver, could even minimal complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity result in some hepatic injury?

Leaving the topic of hepatotoxicity and turning to immunogenicity, routine samples for anti-tocilizumab antibody testing were collected at baseline and at months 1, 2, 3, and 6 in the pivotal studies, and every

24 weeks in the long-term extensions. In addition to routine testing, patients who experienced an adverse event of potentially immunogenic nature, defined in the study protocol, or patient who discontinued treatment because of insufficient therapeutic response underwent immunogenicity testing. A small proportion of patients tested returned positive for anti-tocilizumab antibodies: 46 out of 2,553 patients, or 2 percent, in the tocilizumab treatment groups of the six-month safety population, and 13 out of 477 patients, or 3 percent, got tested in the long-term extension.

Approximately 6 percent, or 10 out of 159 patients, tested for events of potentially immunogenic origin were positive for anti-tocilizumab antibodies during the six-month controlled period, as were 3 percent, or 2 out of 75, in the long-term extension. Five of these patients had events that resulted in withdrawal, to include

anaphylactic reaction, infusion reactions, and hypersensitivity.

During the six-month controlled period, 14 tocilizumab-treated patients withdrew for reasons ascribed to insufficient therapeutic response and underwent loss of efficacy testing. None of these patients were positive for anti-tocilizumab antibodies. Subsequently an additional 50 patients had withdrawn from the long-term extensions for loss of efficacy. Only one of these patients was positive for anti-tocilizumab antibodies.

In light of the small percentage -- 6 percent -- of patients experiencing adverse events of potentially immunogenic origin, testing positive for anti-tocilizumab antibodies, the majority of patients experiencing acute infusion reactions described here were therefore negative.

A higher proportion of patients in

the tocilizumab treatment groups experience acute -- defined as within 24 hours -- infusional adverse events: 7 to 9 percent versus 5 percent in the placebo or methotrexate groups. And the proportion did increase during the long-term extensions.

However, the majority of these patients were able to continue treatment and did not experience recurrence, and thus discontinuations due to infusional adverse events were uncommon. Of note, six patients experienced clinically determined anaphylactic reactions, all of which resulted in withdrawal. Three were positive for anti-tocilizumab antibodies; one was negative; two were not tested.

Anaphylactic reactions tended to occur after the second to fourth infusions. Overall, immunogenicity and acute infusional adverse events occurred in a small fraction of patients who received tocilizumab treatment and did not appear to significantly

impact the overall efficacy or safety profile of tocilizumab treatment. The frequency and severity of these events appear to be consistent with those observed with currently approved biologic treatments for RA.

This table describes an estimate of the potential benefit versus potential risks of tocilizumab treatment in RA. The number needed to treat and number needed to harm calculations were based on the placebo-controlled studies, excluding the non-inferiority study 17824, and utilized the comparison of tocilizumab 8 mg/kg plus DMARD versus placebo plus DMARD from the six-month controlled period.

During this period, the frequency of malignancy diagnoses and lipid-lowering agent starts was the same in the tocilizumab group as for the placebo group, resulting in a number needed to harm of infinity.

As a caveat, it should be noted that the proportion of patients experiencing

malignancy, serious adverse events, serious infections, or needing to start lipid-lowering agents all increased over the duration of the long-term extension studies. However, exposure-adjusted incidence of malignancies remained similar to the controlled period, and exposure-adjusted incidence of serious infections was lower. The rate of GI perforations may be slightly elevated over background rates in RA; however, they were still an uncommon occurrence.

Liver enzyme abnormalities were relatively common. In most cases, liver enzyme elevations were mild to moderate, and no cases of clinically evident hepatotoxicity occurred. As previously noted, a single case of a patient with liver enzyme abnormalities meeting Hy's law criteria was observed and may portend an estimated one serious liver injury case per 47,000 treated patients.

Based on the results of the five

controlled RA trials submitted by the applicant, treatment with tocilizumab resulted in statistically significant increases in clinical responses in patients with moderately to severely active RA.

The safety data from these trials and long-term extensions and the global experience with tocilizumab overall depict the profile of an immunosuppressant and its inherent risks, such as serious infections. Perhaps unique to its mechanism of action, tocilizumab manifested effects on white blood cell count, lipids, and most significantly, liver enzyme elevation, although these were not associated with clinical adverse events in the controlled setting of the clinical trial experience.

Malignancies, GI perforations, and demyelinating adverse events were observed in the clinical trials; however, the relative risks and the role of tocilizumab treatment in the development of these adverse events is

not well defined. The clinical trial experience has been extensive, but may not capture the full extent of safety concerns that may arise with long-term IL-6 inhibition. The decision to approve and the optimal patient population for treatment requires careful balancing of the benefits and risks. This concludes my presentation.

Thank you.

DR. WILLIAMS: Thank you, Dr. Okada. Questions from the Committee to Dr. Okada or the FDA? Dr. Weisman?

DR. WEISMAN: Sarah, if you assume that liver reactions are either idiosyncratic or mechanism-based -- I'm not sure that's entirely fair, but that's a good working definition -- do you consider the liver reactions with tocilizumab to be mechanism-based, and if so, is there an increased risk with the use of methotrexate, which is also presumably mechanism-based as well?

DR. OKADA: Well, as I mentioned, the

mechanism might not be ascertained, but my own personal feeling is that it's likely to be mechanism-based, and the risk of hepatotoxicity, or at least elevated liver enzymes, appears to be increased when it's combined with methotrexate.

DR. WILLIAMS: Dr. Felson?

DR. FELSON: So Sarah, that was a lovely, comprehensive review of stuff, and I wanted to ask you about lipids. And I was surprised that lipids took the back seat in a lot of your concerns. As I looked at these data, they were my primary concern, to be honest. They were my primary concern because rheumatoid arthritis patients are older, and their major cause of death, I think, is still cardiovascular mortality.

And we're talking about something that probably increases their risk of cardiovascular mortality. And given the history of this Committee and Vioxx and other things, I think I would be very leery of

inaugurating a new drug that did that. So I don't have a sense of the magnitude of the lipid changes that occur here and how clinically important they are, and whether such changes have been seen by the FDA in other drugs in front of it for approval for other disorders, and what they've done with that. I guess I want to get a sense from you of whether I should be worried or not, and have you reassure me one way or the other.

Personally, if you told me that I had the choice of a variety of different biologics to use for my patients, all of which had shown efficacy similar to this, and all of which had shown infection risks similar to this, and one of them could kill one of my patients because they raised their lipids and caused an MI, and that the data presented for approval weren't sufficient to determine that, I think I wouldn't prescribe the one that raised lipids, that raised LDLs. Can you comment a little on that concern?

DR. OKADA: So I think the main thing that reassured me -- and granted, it's sort of limited-duration exposure -- but the main thing that reassured me was that during the clinical trials and long-term extensions so far, the rates of significant cardiovascular events was below the background rate that was expected in RA patients.

DR. FELSON: But wasn't that true of Vioxx -- I mean, all of those other drugs came in, probably with bigger datasets than this, and found nothing because there just weren't sufficient numbers yet.

DR. OKADA: That's a valid point, and I think that the sponsor actually has some further additional cardiovascular studies planned. My feeling also, though, is that the changes in lipid parameters were ameliorated relatively easily by statin, concomitant statin therapy, and RA patients are likely to be on statin therapies for multiple other reasons, as you suggested.

DR. WILLIAMS: Dr. Siegel has a comment on this issue.

DR. SIEGEL: Yeah. David, I think your comments are very well-taken, and this is one of the issue we really would like the panel to address. I think our approach here has been that when the initial data came in on lipids, there was an effect on increasing LDLs, but there was also an effect on increasing HDLs, so it was hard to know exactly what the net effect of those changes that go in opposite directions would be. So we decided to take an empiric approach and to follow it along, and to see what the implications were for clinical cardiovascular events.

The other point that I would make is that while lipids are important in predisposing patients to cardiovascular events, there's evidence that inflammatory states may also play a role, based on the increase in risk in patients who have elevated CRP levels. So again, it's hard to

know, based on general principles, how this particular product would work. So in summary, we've taken an empiric approach, and so far, as Dr. Okada has said, we haven't seen an increase in risk, but we would be very interested in hearing from the Committee what additional assessments you think should be done.

DR. WILLIAMS: Ms. Aronson?

MS. ARONSON: To follow up on that, as I read through the sponsor's information -- I can't put my hands on the chart -- of inclusions in the study, I see that patients with infections were excluded, liver disease, and is it that only 87 percent had -- what's the relationship to heart issue in that? Can you answer that question? Exclusion in the trial -- previous heart problems.

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: The number of patients who were excluded for cardiovascular reasons is less than 1 percent. Is that the question?

MS. ARONSON: Less than 1 percent.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: I think this relates to Dr. Siegel's point. This is an agent that can increase lipids but lower CRP. As we discuss this problem, which do you think is more predictive of cardiovascular, low CRP or higher lipids?

DR. OKADA: I need my Karnac hat. If I were going to guess, my guess would be that treatment with tocilizumab -- the risks with respect to cardiovascular events probably could be mitigated with appropriate clinical monitoring and care.

DR. WILLIAMS: Dr. Turk?

DR. TURK: Thank you for that presentation. A quick question for you. You gave us the numbers needed to treat and numbers needed to harm for the 8 mg. Have you calculated those for the 4 mg?

DR. OKADA: I did not; sorry. I could do that real quick if you want.

DR. WILLIAMS: Dr. Hoffman?

DR. HOFFMAN: One of the conclusions that you made is that tocilizumab appears to be effective for patients with moderate to severely active RA, but we have also heard from the sponsor that the agent is also apparently effective in early RA. So I was curious why the FDA, as well as the sponsor, is looking at an indication only for moderate to severely active RA rather than generically RA. Is this a matter of strategy and the approval process, or is this based upon other considerations?

DR. OKADA: Well, actually, if you looked at the baseline disease activity, even in the early RA studies, the patients were moderately to severely active.

DR. HOFFMAN: And realizing that we don't have the data, is there a biologic reason to assume that this drug is not active in early RA? Or we just don't have the data?

DR. OKADA: No, it's been demonstrated to be active in study 17824. However, I think

the distinction is, when we say moderately to severely active, we're talking purely about baseline disease activity. We're not really talking about duration of RA and refractoriness of RA per se.

DR. WILLIAMS: Dr. Siegel has a comment.

DR. SIEGEL: Let me just provide some comments about the regulatory framework here in terms of early RA and late RA and moderately to severely active. When we first started assessing immunosuppressive biologics for RA, we were very concerned about what the toxicities might be, and we thought it was very important, until we knew more about what the safety would be, to restrict the product to people who really needed these.

And we did those in two ways. One is by making the indication for moderately to severely active RA, so patients with mild RA wouldn't be treated, but also to make it in patients who had no other choice, so people

who had already failed all available therapies, which at the time was really confined to methotrexate. As time has gone on and we've gotten more experience with use of the TNF blockers, for example, we have a much better feeling for what the safety is, and we no longer think of it as necessary to require restriction to people who've failed all available therapies, but rather think it should be done based on the risk benefit for the individual patient.

Now, if we had a product that we were thinking about where there were big open questions about what the safety was likely to be, and we thought that there might be a lot of toxicity, that would be a situation where we might well restrict it to people who'd failed all other agents. So I guess the point I'm trying to make is, early versus late -- we haven't seen evidence that products that work in late disease don't similarly work in early disease. The big

question is what the risk benefit is.

DR. WILLIAMS: Dr. Stine?

DR. STINE: Thank you. I just had a couple of short questions. Have you looked at co-occurrence of any of these adverse experiences? Or do you look at them one at a time, so we'll see a table of this many people had liver, this many people had that, this many people had a different one. Is there any evidence that these things happen together, that there's some people that tend to get a whole collection of these things at once, or are these things just sort of at random?

DR. OKADA: I have to be honest that in most of the displays that I've looked at in the application, the effect of tocilizumab on, for example, laboratory parameters, was displayed individually, understanding that patients could have more than one laboratory abnormality at a time. But I don't know the details to answer that question, so I'm not sure I can --

DR. STINE: I was thinking more on the AE side -- the people that have the liver problems also have the --

DR. OKADA: I see what you're saying.

DR. STINE: Yeah.

DR. OKADA: Well, looking at the adverse event profiles by patient, there are of course some patients who have several adverse events and other patients who only have it sporadically. I can't say that I detected a particular pattern.

DR. STINE: Yeah, I was just trying to get a sense. When we look at these counts of adverse experiences and you try to extrapolate to a larger population, you wonder how many people are going to be affected, and I think it's important to understand that we just add these numbers up if, in fact, they co-occur. It's the same person, perhaps, having a lot of these things, and that's not good for that person, but it's fewer people that would be affected. If I can just sort of continue on

this theme for just two more questions, what's the uncertainty -- I'm not too familiar with this term that you use, number needed to treat and number needed to harm -- but I gather there's some considerable uncertainty in these estimates? I mean, you've got a number here for 385 for GI perforations and seven for liver enzyme abnormalities. And I was wondering, is that seven plus or minus a thousand? Seven plus or minus two?

Seven plus or minus about how much?

DR. OKADA: No, that was rounding up to the whole integer.

DR. STINE: Right. But I want a standard error that goes on that number, a confidence interval.

DR. OKADA: That, I can't give you.

DR. STINE: Okay. And then one last question. You guys are worried about liver things, and I've taken some of these things, and they'll check my liver. But this demyelination stuff, that's the one that bothered me

personally. What's the background rate for that in the population as -- I know you don't know it for RA -- but what is it in the population as a whole? Do we have anything on -- does this stuff never happen, or only here?

DR. OKADA: It's extremely uncommon, but I honestly don't know what the rates would say. For example, multiple sclerosis -- I don't know if we have any neurologists here.

DR. STINE: So we don't know.

DR. WILLIAMS: Dr. Rappaport?

DR. RAPPAPORT: Well, just because I'm a neurologist doesn't mean I have that number off the top of my head, but we can certainly find that number for you. Multiple sclerosis is the main central demyelinating disease, and it is not uncommon, and it depends on what part of the world you live in.

DR. STINE: Uh-huh. The reason for my concern was that I can imagine when you get a blood test for taking things, they check liver, they check this; they don't check that. And I

wouldn't think that would be something that the physician might be accustomed to looking for, and it's severe enough that you would certainly want to have some sense of the risks involved.

DR. WILLIAMS: Dr. Pisetsky?

DR. PISETSKY: The question relates to the issue of immunogenicity. And some of the patients here had been previously treated with TNF. Is there any relationship between prior treatment with a biologic or an adverse reaction and then an adverse reaction with this product, and then correspondingly, if someone develops an antibody or a reaction to this product, would that be predictive of a problem with another antibody?

DR. OKADA: What I can tell you is, based on what I see of the overall safety profile, patients who are more refractory and sicker tended to have increased incidence, as you might expect, of adverse events. I didn't see any relationship with immunogenicity per se. But the anti-TNF subgroups, particularly those

who've been exposed to multiple TNF therapies, is relatively small. So it's hard for me to draw definitive conclusions on that.

DR. PISETSKY: Does an adverse reaction or an infusion reaction to another biologic raise an issue in this population?

DR. OKADA: I am not sure how many of the people who experienced infusion reactions had infusion reactions with previous biologics.

DR. WILLIAMS: I'd remind the Committee you're now using your lunch hour.

Dr. Felson?

DR. FELSON: Oh-oh. I have a question for you. It sounds like this agent is already approved in Japan. Has there been widespread use in Japan? I mean, the struggles we're having here are, as Dr. Stine said, coming up with confidence bounds around estimated rates, basically. We can't figure out whether we should be worried or not because there just aren't enough numbers. Are there more number we can get from Japan that we can take advantage

of?

DR. OKADA: Well, the product was only approved in Japan for RA and the pediatric JIA indications in April of 2008, so I am not aware of the post-marketing experience there. The pre-marketing experience was smaller than the data presented here, so I don't know if the sponsor has anybody who's aware of --

DR. WILLIAMS: Dr. Fletcher?

DR. KRASNOW: If you want to -- we have a representative from Chugai who can comment if you would like.

DR. WILLIAMS: We'd like to hear.

MR. OKUDA: My name is Osamu Okuda, Chugai. And tocilizumab was approved for RA in this April 2008. So far, we have treated the patients -- the number of patients are -- 1400 patients have been treated with tocilizumab. So -- and no new safety signal has been detected so far.

DR. WILLIAMS: Thank you.

Dr. Fletcher?

DR. FLETCHER: Yeah, I was wondering whether the sponsors provided FDA any information about intermittent dosing, with a hiatus of treatment, say, more than five half-lives of the drug, with regard to -- I know I'm kind of hammering this -- but the immunogenicity aspect and anti-drug antibodies? Long-term, you're obviously going to be looking for that, but in the past there's been issues with intermittent use where a significant hiatus has been associated with some safety issues when reinitiating. And I was wondering did they have any data on that?

DR. OKADA: The sponsor provided some data in the application regarding patients who missed doses or had an extended duration between completion of the core studies and long-term extensions. And overall it didn't appear that that significantly impacted immunogenicity.

DR. WILLIAMS: Dr. Sandborg?

DR. SANDBORG: Have there been any studies of this agent in inflammatory bowel

disease?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Our Chugai colleagues will respond. They've done studies in different indications than we have.

MR. OKUDA: The answer is yes. We have conducted a very small pilot study in Crohn's disease. The number of patients studied is 36.

DR. WILLIAMS: We'll now break for lunch. The open public hearing is scheduled for 12:45.

I would remind the Committee that discussions of the presentations should only take place in the open forum.

Thank you.

(Whereupon, at approximately 11:53 a.m., a luncheon recess was taken.)

A F T E R N O O N  S E S S I O N

(12:46 p.m.)

DR. WILLIAMS: We will now begin the open public hearing. Both the Food & Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its products, or, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at

the beginning of your statement to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this Committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

We have had two people register to

speak at the open public hearing. We will first hear from Susan Karder.

MS. KARDER: Hi. My name is Susan Karder. I was diagnosed with RA when I was 36, and I've been suffering with it for 7 years. I'm here today because looking at me now, you would not believe I have RA, and this is thanks to Actemra. I do not own stock in Roche, and I have been paid only minimal compensation for my time, travel, and expenses.

My disease started out with severe pain that traveled throughout my body that would leave me debilitated for days on end. On the day I went for blood work for diagnosis, my husband had to dress and drive me because I could not lift either of my arms. The diagnosis came back as an aggressive form of RA. RA runs in my family, as my grandmother suffered with it for years.

Upon diagnosis, I did some research, and I found out that the average person becomes totally disabled within 10

years of diagnosis. To think I had 10 years in which to finish raising my boys and to secure my financial future was truly terrifying and overwhelming.

My doctor prescribed a litany of drugs for me, including prednisone, Celebrex, Bextra, Vioxx, and finally weekly injections of Humira with methotrexate. While I felt relief with the Humira, I did get severe injection site reactions that were huge welts that would itch and burn and would last for a whole week.

Unfortunately, at this time I did lose my job, and eventually my insurance and my financial way of paying for any drugs to help my disease. We moved to Arizona in hopes the climate would help me.

Unfortunately, it didn't, and I became like a turtle on my back, unable to do anything to help myself or my family. At this point, my husband wrote to the University of Arizona and asked them if there

were any programs I could participate in that would help me. I met with a study doctor and was accepted into an MRA study. For the first four months of the study, I felt no relief. They put me into what they call a rescue program, where I knew I was going to get 8 mg of Actemra. Within the first infusion, I felt relief instantly. It was amazing.

I went from being unable to get off a couch without assistance to being told to slow down when we went shopping. It was just amazing. Before Actemra, I was just existing. After Actemra, I started living again.

My fear of being disabled is gone. Actemra needs to be approved. It's too late from my grandmother, who died from the steroid treatments that were available to her in her time. But it's not too late for me or my niece, who's 18 years old and was just told she's at high risk of developing RA.

Please secure my healthy future, my niece's future, and the future of all those who have RA by approving this drug.

Thank you.

DR. WILLIAMS: Thank you, Ms. Karder. Ours second speaker will be Phylicia Melugian, and I hope I got your last name right.

MS. MELUGIAN: Yes, you did, thank you. My name is Phylicia Melugian, and I'm 47 years old, and I've had RA for seven years. I'm here today to urge you to recommend approval for Actemra. I do not own stock in Roche, and I have received only minimal compensation for my time, travel, and expenses.

I'm here today because my life is so much better since taking Actemra and because I want this drug available so that I can stay this way. Before my diagnosis, I experienced a level of pain in my shoulder. It lasted over several days. And I have a pretty high threshold for pain, but this pain became unbearable. For someone who has never

had RA, it's like a red-hot poker being jabbed between your joints. I thought the pain was from a pulled muscle or overexertion, and I couldn't figure out anything that I had done wrong to cause this.

Over a six-month period when I was trying to figure out what was wrong, I went to the emergency room and was sent home with the doctor telling me there was nothing wrong. My doctor finally tested me for RA, and I tested positive. It terrified me because I didn't know what to expect. After all, arthritis was something my grandma had; I was only 40.

I was put on one drug after another: Celebrex, methotrexate, Mobic. Nothing worked. I had gone from being a very productive and active person to not being able to do anything. The fatigue was physically and emotionally debilitating.

Then I found out I was pregnant with twins. I was thrilled and terrified at

the same time, especially finding out there were two, because I was worried because I couldn't take care of myself, let alone take care of two babies. During my pregnancy, the RA seemed to become dormant, but what if the RA came back?

My babies were born in October of 2001; I was blessed with a son and a daughter. And everything was going fine until they were about seven weeks old, and then the arthritis came back with a vengeance, way worse than before. I couldn't pick up my babies or hold them in my arms because my wrists were too swollen and painful to pick them up, and I was afraid I'd drop them. I had to have help with the most basic of things: I couldn't open a jar or a can or lift a coffeepot; I couldn't hook my own bra or even hold a hairdryer. I couldn't take care of myself, let alone my family.

I consider myself to be a fairly happy, upbeat person, but when you hurt like

that you feel totally defeated, and you feel like you want to toss in the towel.

I went to my rheumatologist in tears, and that's when he suggested joining a test study. A month later I received my first infusion. I didn't know if I was getting the drug or not, but immediately after my second infusion, the difference was amazing, absolutely amazing. I started doing things again I hadn't done in a long time. I could hold my babies in my arm; I could rock them in a rocking chair; I could go for a walk just for fun. I could work in my flower garden again. I didn't have to crawl on the floor any more.

Now I do what I want when I want, and my now six-year-old twins -- well, they think it's pretty cool that momma can show them how to do a cartwheel. Now I keep up with their school and PTA and sports and family and friends, and the quality of my life has improved 100 percent. I don't live

in fear of the disease any more. I live in fear that I won't be able to get the drug. Please don't take Actemra away. Thank you.

DR. WILLIAMS: Thank you, Ms. Melugiann. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The sponsor has requested some time to respond to an issue that was raised in the last presentation and with the following discussion.

You have five minutes.

DR. KRASNOW: Thank you. We have two points for clarification: One related to cardiovascular and the other related to the "potential Hy's case." And I'd like to invite Dr. Paul Watkins to comment on the case.

DR. WATKINS: Hello. I'm Paul Watkins. I'm a professor of medicine, a hepatologist with a long-term interest in drug-induced liver injury, both clinical and mechanisms that underlie drug-induced liver injury. I was on a safety monitoring board with

two other experienced hepatologists that monitored the liver events throughout the Phase III studies, and I've had the opportunity to query the database in the last several months. And I've been very interested in this compound because of the multiple roles IL-6 has in liver and hepatocyte biology. And overall, really the database is very reassuring in terms of liver safety.

There is one case that was mentioned as the Hy's law case. If you look at the bottom, starting here at day 239 of treatment with TCZ, you can see that the elevations in ALTs were first noted. Or rather -- sorry -- 218 the ALT was first noted at 137. That then increased to about 16 times the upper limit of normal, and at this time the total serum bilirubin was at more than two times the upper limit of normal. Now, this is what's called Hy's law, as you heard. And the idea is, we really don't know what to make out of isolated

asymptomatic ALT elevations, but if they're accompanied by signs of the liver not functioning -- and bilirubin elevation's on that basis -- that is thought to be a very reliable sign of a drug with potential to cause liver injury.

However, you'll notice that the indirect bilirubin is the predominant form of bilirubin that is unconjugated, that's elevated. Normally, you would expect in a true Hy's law case to have about equal direct and indirect. So this suggests Gilbert's syndrome. However, what really, I think, clinches the diagnosis is that earlier in treatment -- here we're at day 98, 113, 141 -- when the serum ALT and AST were entirely normal, there also was elevation in indirect bilirubin. This is different units.

This is going from the six months to the long-term extension, but the upper limit of normal is 21 micromoles, and you can see over 30 micromoles of indirect bilirubin.

So at a time when there was no evidence of liver injury, this person had an indirect hyperbilirubinemia. This is essentially diagnostic of Gilbert's. So by the draft guidance criteria, which were shown to you in the FDA presentation, this case would not be considered a Hy's law case. And therefore the extrapolation for severe liver injury -- it's not appropriate to base that on this case. Thank you.

DR. KRASNOW: In our remaining one and a half minutes, I would like to ask Dr. Sattar to put in perspective --

DR. ROSEBRAUGH: Could I interrupt for just a second?

DR. KRASNOW: Sure, sure.

DR. WILLIAMS: Dr. Rosebraugh.

DR. ROSEBRAUGH: Right. I just kind of want to make a couple of points. It is a little bit difficult when we're trying to sort out whether something is Gilbert's disease or not. The point I would make is, in the agency

we usually like to see a consistently high bilirubin before the drug is started before we would consider it being Gilbert's.

Additionally, when the bilirubin -- if it goes up at the same time as ALT, that tends to indicate that it is more of a drug-induced effect and not on the basis of Gilbert's.

Additionally, I would say that when we are looking at ALTs, if we have three times the normal ALT level, we don't get too shook up about that; there's a lot of drugs that do that. When we start to get 8 and 10 times, our eyebrows start to go up.

If something causes ALT to go up 16 times, our eyebrows start to meet our hairlines. So I think that I would view this as a Hy's law case because of the reasons I stated, that they had a normal bilirubin at day one -- 91; it went up in conjunction with the ALT going up; came down when the ALT came down; and went back up on the re-challenged.

DR. WILLIAMS: Thank you. You still have your minute and a half.

DR. KRASNOW: Thank you very much. I would like to ask Dr. Sattar to put in perspective some of the changes we've had within the cardiovascular markers.

DR. SATTAR: Thank you very much. I'm Naveed Sattar. I'm Professor of Metabolic Medicine at University of Glasgow. I think this is a -- the lipid changes in RA, I think, with respect to an earlier question, this is an important concept. The paradigm in RA in terms of lipid changes is somewhat different than the general population. If you consider the inflammation in man, it generally reduces lipids whether you're post-MI, post-surgery, whether you have sepsis. The lowest cholesterol levels you will ever see are in patients in ITU therapy.

In ITU therapy, cholesterols go down to 1 millimole per liter. In cancer you can get low cholesterol in RA. And

generally, in all these populations, the higher the inflammation, the lower the lipid levels. And also in general, when you have resolution of the inflammation spontaneously over treatment, lipid levels go up -- HDL, LDL, triglycerides.

And the other clincher, I think, in terms of RA is that there is now emerging evidence from at least 10 to 12 studies that TNF blockers raise lipids up to 24 percent, including cholesterol and HDL -- and less so to DMARD. And in particular, responders to TNF blockers also have raised lipids as well. And as you know, the TNF blockers in general -- we believe as a community that TNF blockers are probably counterprotective, particularly in responders.

Two more slides, just to prove that the lipids do go up with TNF blockers I think is an important concept. This is from a couple of years ago, but effectively, most of the data is from infliximab throughout these

small studies. But here, for example, you can see in study one, LDL goes up by 20 mg/dL. And in that particular study, that was a 24 percent rise in LDL. And that's reasonably consistent. If you go back and look at the literature now, there are probably about 10 studies that show that TNF blockers (inaudible) look back retrospectively, raise lipids.

And one last slide. And the other concept, therefore, is that -- here's a couple of studies for example, infliximab six-month -- the more cholesterol went up -- in this case more than HDL, but generally it's varied; in some, HDL goes up more, others total cholesterol. The key concept here is, the more the DAS went down, the more the lipids went up. And it's the same with (inaudible).

The more the DAS went down, the more both total cholesterol and HDL went up. So the paradigm, I think -- the key point

here -- in the context of high inflammation like RA, lipids go down, and with resolution of inflammation with TNF blockers and with IL-6, lipids go back up.

So I think to interpret lipid changes in the normal fashion, I think, may be slightly erroneous, but I think the sponsor is taking a responsible attitude by looking at cardiovascular and by also advocating statin treatment. So I think they're taking a very concerted approach, which I think is balanced. Thank you.

DR. WILLIAMS: Thank you. The Committee will now turn its attention to address the task at hand: The careful consideration of the data before the Committee as well as the public comments. I would inform the Committee that we have four questions. The first one has to do with safety, the second one with dosing. The third is a vote on whether or not we recommend approval, and the fourth question depends on the result of that vote.