FOOD AND DRUG ADMINISTRATION

ARTHRITIS ADVISORY COMMITTEE

MEETING

Silver Spring, Maryland

Tuesday, July 29, 2008

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P R O C E E D I N G S

(8:29 a.m.)

DR. WILLIAMS: We welcome you to this Arthritis Advisory Committee meeting. I'm James Williams, and I am the acting chair of this meeting.

For topics such as those being discussed in today's meeting, there are often a variety of opinions, some of which are strongly held. Our goal in today's meeting is to have it be a fair, open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their

conversations about the topic at hand take place in the open forum for the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. We'd like to introduce the members of the Committee.

I will ask them to introduce themselves with their name and institution. I'll begin with Dr. Fletcher.

DR. FLETCHER: Good morning. I'm Mark Fletcher. I'm the industry representative for this Advisory Committee. My background training is in allergy, immunology, and rheumatology, and I presently work for Pfizer in an internal consulting function as an immunovaccinology consultant. Thank you.

MS. MALONE: Hi, I'm Leona Malone.

I'm the patient rep. I've had rheumatoid arthritis for 42 years. Thank you.

DR. FELSON: Hi, I'm David Felson. I'm a rheumatologist and epidemiologist from Boston University.

DR. PISETSKY: David Pisetsky, rheumatologist and immunologist from Duke University.

DR. HOFFMAN: Gary Hoffman. I'm a rheumatologist from the Cleveland Clinic.

DR. BLUMENTHAL: David Blumenthal. I'm a rheumatologist with the Case Western Reserve University and MetroHealth Medical Center in Cleveland.

DR. SANDBORG: Christy Sandborg. I'm a pediatric rheumatologist from Stanford University.

DR. WILLIAMS: James Williams. I'm a rheumatologist from the University of Utah.

DR. VESELY: Nicole Vesely, designated federal official, Arthritis Advisory Committee.

DR. TURK: Dennis Turk, from the

University of Washington in Seattle. I'm a specialist in clinical trials and outcome measures.

DR. STINE: Robert Stine. I'm a statistician at the University of Pennsylvania.

MS. ARONSON: Diane Aronson, consumer representative. I've served as such with the NIH, CDC, and for the FDA on laboratory oversight in previous times.

DR. WEISMAN: I'm Michael Weisman, a rheumatologist from Cedars-Sinai Medical Center in Los Angeles.

DR. OKADA: Sarah Okada, rheumatology clinical team leader for FDA.

DR. SIEGEL: Good morning. I'm Jeffrey Siegel, team leader in the Division of Anesthesia, Analgesia and Rheumatology Products at the FDA.

DR. RAPPAPORT: Good morning. I'm Bob Rappaport. I'm the division director for that division.

DR. ROSEBRAUGH: Curt Rosebraugh,

director, Office of Drug Evaluation II.

DR. WILLIAMS: Thank you. We will now turn the microphone over to Nicole Vesely.

DR. VESELY: The Food and Drug Administration is convening today's meeting of the Arthritis Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the Committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug & Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and

temporary voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to

them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contract, grant, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves Biologics License Application 125276, ACTEMRA, tocilizumab, sponsored by Hoffmann-LaRoche, Inc., part of the Roche Holdings, Ltd., for the proposed treatment of adult patients with moderately to severely active rheumatoid arthritis.

This is a particular matters meeting during which specific matters related to Hoffmann-LaRoche's ACTEMRA, tocilizumab, will be discussed. Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of

interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Mark Fletcher is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. His role at this meeting is to represent industry in general, and not any particular company. Dr. Fletcher is employed by Pfizer, Inc.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have

with any firms at issue. Thank you.

DR. WILLIAMS: Thank you. We'll now have some opening remarks by Dr. Jeffrey Siegel.

DR. SIEGEL: Thank you, Dr. Williams. Good morning, and welcome to this meeting of the Arthritis Advisory Committee. As you heard, we convened this panel in order to discuss the licensing application from Hoffmann-LaRoche to market tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis.

Tocilizumab is a monoclonal antibody directed against the IL-6 receptor. As such, it has a novel mechanism of action. As you know, rheumatoid arthritis is a chronic inflammatory arthritis. When left untreated or inadequately treated, it can lead to debilitating effects in patients.

Fortunately, over the last decade, a number of new advances in the field have substantially reduced the burden of disease on patients. Many of these advances have

come from the approval of new products for rheumatoid arthritis that have benefits in patients who hadn't responded to therapies that were previously available. Nonetheless, even with the most effective of these products, some patients don't respond, and many patients don't respond completely.

Hoffmann-LaRoche has conducted clinical trials with tocilizumab in the treatment of rheumatoid arthritis. In the presentations this morning, you'll hear a discussion of the findings with respect to efficacy and safety from Hoffmann-LaRoche.

In the agency presentation, you'll hear only a brief discussion of efficacy, because there are not major disagreements between the FDA and Hoffmann-LaRoche on what the efficacy findings are. In contrast, our presentation will focus on the safety findings and safety concerns that we uncovered in review of this application.

In our questions to the panel that

you'll be considering this afternoon, we are particularly interested in hearing your thoughts about the safety concerns that you have on review of the data. We would like you to keep in mind that the safety findings that are observed during the clinical trials may not fully anticipate the safety of a product that's seen after the product is approved. This can occur for a number of different reasons. For one, the number of patients who are exposed after a product is approved is typically much greater than the number who are exposed during clinical trials.

In addition, the patients who receive the product after the product is approved may differ in important ways in terms of the concomitant medical conditions they may have, the concomitant medications they may be on, and the degree of monitoring that's typical for clinical trials as compared to typical clinical practice. We

ask you to take this into account in your considerations.

Finally, we will be asking you to consider the potential benefits of the product against the potential risks, to provide your opinion about whether this product should be approved for this indication.

So with that, I thank you, and we look forward to your deliberations.

DR. WILLIAMS: Thank you. We will now turn the time over to the sponsor for their presentation. The sponsor is Hoffmann-LaRoche, and they will begin with an introduction and overview by Dr. Jonathan Leff.

DR. LEFF: Good morning. I'm Dr. Jonathan Leff from Roche. Thank you to the Arthritis Advisory Committee as well as the FDA for the opportunity to present the tocilizumab clinical program.

The proposed indication for ACTEMRA or tocilizumab is for reducing signs and

symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs or TNF antagonists, or in whom DMARDs are not considered appropriate.

ACTEMRA can be used alone or in combination with methotrexate or other DMARDs, and should not be used in combination with other biologics.

The recommended dose is 8 mg/kg intravenously once every four weeks. As general dosing advice, 8 mg/kg is consistently more efficacious than 4 mg/kg in a range of RA patients.

Reductions from 8 mg to 4 mg/kg may be considered for management of dose-related laboratory changes, including elevated liver enzymes, neutropenia, and thrombocytopenia. In DMARD inadequate responders, 4 mg/kg may be considered, followed by an increase to 8 mg/kg based on clinical response.

We are here to discuss tocilizumab,

which, as mentioned, is a humanized monoclonal antibody with an IgG1 construct. It binds both soluble and membrane-bound Interleukin-6 receptors. It has weak or no CDC or ADCC effector functions. Competitive inhibition of Interleukin-6 suppresses inflammation both systemically and within the joint.

IL-6 is produced by multiple cell types, and is associated with numerous biological activities, affecting many relevant cells, including hepatocytes, which mediate the acute-phase response, as well as osteoclasts, B-cells, T-cells, and macrophages. In addition, IL-6 itself suppresses cytochrome P450 levels, which may affect metabolism of various drugs.

In fact, inhibition of Interleukin-6 activity may explain some of the laboratory changes seen in the program, either as a pharmacodynamic effect or an adaptive change.

Within the joint, IL-6 has numerous articular effects in RA, including again numerous cell types, including the synoviocytes, endothelial cells, osteoclasts, T-cells, neutrophils, macrophages, and B-cells. These effects are pro-inflammatory and cause marked inflammation within the joint.

As for Interleukin-6, it competitively binds both to membrane-bound and soluble receptors, and I'll demonstrate that here. Seen here is the membrane-bound Interleukin-6 receptor, which binds to Interleukin-6, forming a complex which then associates with two gp130 co-receptors on the membrane. This complex then activates the cell, causing signal transduction.

These membrane-bound receptors are found on hepatocytes, neutrophils, and a subset of T-cells. Additionally, Interleukin-6 can interact with a soluble IL-6 receptor, and this soluble IL-6 receptor

is usually formed via cleavage of the membrane-bound receptor. It is then soluble and can bind similarly to Interleukin-6, again causing the same complex, which again can associate with two gp130 co-receptor molecules, even on cells that do not bear the Interleukin-6 receptor. Notably, most cells do bear gp130 on their surface.

Tocilizumab blocks the interaction of IL-6 with either one of these receptors, blocking IL-6 signal transduction via both pathways.

Tocilizumab behaves like most monoclonal antibodies. The AUC, C-max, and C-min are as you see here.

The greater exposure on 8 mg shown here with AUC leads to a greater and more persistent suppression of inflammation over the course of the entire dosing interval. The half-life varies by dose, from 2 to 11 days at the 4 mg/kg dose, and from 4 to 13 days at the 8 mg/kg dose. It is metabolized

in the usual way for antibodies, via proteolytic digestion. Monitoring of drugs that are metabolized by cytochrome P450s, with a narrow therapeutic index where the dose individually adjusted, is advised.

Again, as mentioned, the anti-TNF agents in particular have been a welcome advance in the treatment of rheumatoid arthritis. They were the first therapy since methotrexate to dramatically improve signs and symptoms, including radiographic responses. Now we have B-cell therapies, which are another mechanistic option for some patients, as well as selective modulation of co-stimulatory activation for others. But we are not where we need to be. Remissions remain elusive. ACR 70s are rare. Even ACR 50s are only seen in about 50 percent of patients. Moreover, some patients that initially respond lose that response over time.

Rheumatoid arthritis is a lifelong

disease. Patients will be cycling on and off therapies for many years, and they need options. Clearly, there is a need for new therapies, with unique mechanisms of actions, to add to our armamentarium.

Tocilizumab is a joint development program with our partner, Chugai Pharmaceuticals. It is approved in Japan for the treatment of adult rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, and polyarticular JIA, for reducing signs and symptoms and inhibition of progression of structural joint damage. Patients have been treated in the Chugai program with tocilizumab for up to five years. It is also approved in Japan for Castleman's disease.

We have conducted a broad clinical program in three distinct populations. After initial dose-ranging studies, we conducted a large study in patients with an inadequate response to anti-TNF agents. We have also conducted three large studies in patients

with an inadequate response to methotrexate or DMARD.

Notably, one of these studies, the 823 study, is a radiographic study, the results of which have recently become available and will be shared with you later this morning. Please be aware that FDA has not yet reviewed this data.

We also have studied a monotherapy study in patients with limited or no methotrexate exposure. We are currently following over 2,500 patients in long-term extensions. Notably, 94 percent of those patients who are eligible for enrolment elected to do so, and the dropout rate has been low. In addition, we have an ongoing pediatric program.

We have generated a large safety database with tocilizumab, with over 3,700 patients exposed to at least one dose of tocilizumab, providing a well-characterized safety profile. Over 2,700 patients have

been exposed for six months or more; over 2,000 for one year or more; almost 500 for two years or more. We have somewhat less exposure on the 4 mg/kg dose, at over 500 patients for six months or more. And our control treatment approaches about 1,000 patients, representing placebo or DMARD patients. In addition, we have a robust risk management plan proposed, which you will hear about later this morning.

After my own remarks, Dr. Kenneth Bahrt will review the efficacy profile of tocilizumab, followed by Dr. Joel Krasnow reviewing safety, and then Dr. Philippe Van der Auwera will present the risk mitigation and pharmacovigilance program. And then Dr. Bahrt will come back and summarize.

We have with us a variety of Roche individuals to help answer your questions. And we also have with us three consultants: Dr. Paul Watkins from the University of North Carolina; Dr. Wayne Schwesinger from the

University of Texas San Antonio, and Professor Naveed Sattar from the University of Glasgow.

I will now turn it over to Dr. Kenneth Bahrt.

DR. BAHRT: Thank you, Jonathan. I'm Kenneth Bahrt. I'm the global medical director for autoimmunity at Hoffmann-LaRoche, and I'd like to spend this time going over the efficacy that was demonstrated by tocilizumab in a clinical development program.

We'll do this by first looking at the Phase II dose-ranging study, and then a high-level overview of the efficacy seen in Phase III, and then drill down on the use of tocilizumab in combination with DMARDs in patients who have had an inadequate response to DMARDs and in patients who have had an inadequate response to anti-TNF therapy.

We will then follow this by looking at tocilizumab use in monotherapy, and then have a few conclusionary remarks.

The Phase II program was conducted by our Chugai colleagues in Europe and consisted of a seven-arm study. Three of the arms looked at tocilizumab at 2 mg/kg, 4 mg/kg, and 8 mg/kg in monotherapy. Three other arms looked at tocilizumab at 2, 4, and 8 mg/kg in combination with methotrexate.

And there was a control arm of placebo on a background of methotrexate. This was a 16-week study, with the endpoint of being ACR 20 at week 16.

If we look at the response in those patients who had combination therapy, one can see that 8 mg/kg and 4 mg/kg were particularly effective at the higher ACR endpoints of ACR 50 and 70. And in monotherapy it was the 8 mg/kg dose, particularly with the ACR 50 and 70, that had the better result.

Based upon these results, it was decided to take 8 mg/kg forward in our monotherapy studies in Phase III, and the

8 mg and 4 mg doses forward in our Phase III program in combination with background DMARDs.

As Dr. Leff has said, the clinical program for tocilizumab consisted of five pivotal trials. Four of these trials are completed. One of these trials, the 823 trial, is ongoing through two years of therapy. One year, we just have the data that has recently become available looking at not only signs and symptoms, but also physical functioning and radiographic progression, and these will continue into a second year looking at radiographic progression and physical functioning.

Of those trials that were completed, over 90 percent of those patients were eligible to enter the long-term extensions. Eighty percent of these patients entered the long-term extension coming off their assigned therapies, while 10 percent of these patients entered the long-term

extensions coming off of escape therapy. Of those who were eligible to enter the long-term extensions, over 2,500 patients elected to do so. And over the two years of follow-up so far, only 14 percent of the patients have withdrawn, 3 percent for lack of efficacy, and roughly 6 percent because of adverse events.

In a clinical program as large as tocilizumab, it would not be possible to go over each individual endpoint that was looked at in the clinical trial. However, from this slide, one can see that in the 8 mg/kg group, all of the key primary endpoints and key secondary endpoints were met at this dose.

At 4 mg/kg, the primary endpoint of the ACR 20 was achieved in all clinical trials. And in the 822 trials, all the key secondary endpoints were achieved as well. However, in the 823 and the 062 trial, aside from the primary endpoint and the DAS28 endpoint, no other of the key secondary

endpoints were met.

If we now look at tocilizumab in combination with DMARDs in patients who have had an inadequate response to DMARDS -- this consisted of three of the pivotal trials. The 822 trial and the 823 trial were on a background of methotrexate, and both doses of 4 mg and 8 mg were looked at.

Again, the primary endpoint was the ACR 20 at six months. In the 063 trial, only the 8 mg/kg dose was looked at, and the background medications were conventional DMARDs. However, in this group, 50 percent of these patients were on methotrexate alone, and the other 50 percent of the patients were on either DMARDs alone or DMARDs in combination with methotrexate.

This is the study design of the 822 trial. The patients were screened, their methotrexate was continued, other DMARDs were discontinued, and then they were randomized in a 1:1:1 fashion to receive either

tocilizumab 8 mg/kg, 4 mg/kg, or placebo. It was a six-month trial, with a primary endpoint of an ACR 20. At the end of the trial, the patients were eligible to enter open-label long-term extension, which was tocilizumab 8 mg/kg every four weeks.

In all of the pivotal trials, there were escape mechanisms built in for patients who did not have a response. At week 16, those patients who did not have at least a 20 percent improvement in swollen and tender joints could elect to enter the escape therapy. The escape therapy in most all of the clinical trials was open-label tocilizumab at 8 mg/kg.

The 063 trial was similar to the 822. However, instead of stopping their background DMARDs, their background DMARDs were continued, and then they were randomized in a 2:1 fashion to receive either tocilizumab 8 mg/kg or placebo. Again, this was a six-month study with the ACR 20 as the

primary endpoint. Again, at the end of the trial, these patients were able to enter long-term extension on open-label tocilizumab at 8 mg/kg.

The 823 trial is the ongoing trial, and we'll show data in this presentation from the first six months of that trial. The methotrexate was continued. They were then randomized to a 1:1:1 fashion to receive either tocilizumab 8 mg/kg, 4 mg/kg, or placebo. And the primary endpoint at six months was the ACR 20. These patients were then continued in a double-blind fashion through another 6 months, and at 12 months, an endpoint of structural damage and physical functioning was looked at.

These patients will then continue in open-label fashion for a second year, with again the endpoint at 24 months being structural damage and physical functioning.

These are the baseline characteristics from these three clinical

trials. They are balanced across all of the clinical trials and similar to other clinical trials done in this population. The mean age of the patients was around 50 years old. There was about 9.3 years of disease duration, and all had significant background disease activity, as manifested by a DAS28 of about 6.7. There was approximately 20 swollen and 30 tender joints present, and the mean HAQ was about 1.5.

About 50 percent of these patients were on background corticosteroids, and the mean dose of methotrexate in these studies was about 15 mg per week.

If we look at the disposition of patients from these clinical trials, one can see that over 90 percent of the patients completed the clinical trial on the assigned therapy. Twenty-six percent of the patients on the placebo completed the clinical trial via the escape mechanism, while 16 percent and 6 percent completed via the escape in the

4 mg and 8 mg arms respectively.

As expected, more patients discontinued from the clinical trials because of adverse events on the active treatment arms, and more patients discontinued from the placebo arm because of inadequate efficacy.

If we look at the response for the primary endpoints from each of the individual trials, one can see from the 822 trial that both active treatments achieved the ACR 20, 50 and 70 responses.

From the 823 trial and the 063 trial, it was only the 8 mg/kg arm that achieved all three ACR endpoints.

If we look at those patients who achieved a DAS28 score of less than 2.6, again in the 822 trial, both the 8 mg and 4 mg arm accomplished this endpoint, while in the 823 trial, only the 8 mg/kg arm did so. In the 063 trial, it was the 8 mg/kg arm again that achieved this clinical endpoint.

Because of the similarities in

these clinical trial designs, their baseline characteristic, and the fact that all three clinical trial met their primary endpoint, there was a pre-planned pooling strategy undertaken to look at these clinical trials together so that we could have a better chance of looking at questions around dose and different subgroup populations.

So in the pooled data, for the ACR 20, the ACR 50, and the ACR 70, both active treatments met these endpoints. While each individual study was not powered to look at differences between the active treatment arms, by pooling the data together, we did achieve enough statistical power to look at the difference between doses, and for the ACR 20, 50, and 70, the 8 mg/kg arm was statistically better than the 4.

Also, looking at different subgroup analysis, for the 8 mg/kg group versus placebo, for age, gender, race, region, duration of RA, and whether the patient was

rheumatoid factor positive/negative, one can see that all the point estimates fall to the right of unity, showing that 8 mg was more effective than placebo. The confidence intervals do cross unity for those patients who were greater than 75 years, but I caution you that there were small numbers in this particular group.

If one looks at the 4 mg/kg dose, again, one can see that all point estimates fall to the right of unity, showing that 4 mg was statistically better than placebo. Again, the confidence intervals for those who determined that they were black did cross the unity line. However, again, there were small numbers in this particular group.

We also know that many patients in this group are not treated with methotrexate alone, but a variety of background DMARDs, and in the 063 trial, we looked at the response of tocilizumab against these background DMARDs. And one can see that no

matter what the background DMARD was, or combination of DMARDs, that tocilizumab at 8 mg/kg was better than those who were on the DMARDs alone.

If we look at the response over time for the ACR 20, one can see that with both active treatments, there's a rapid onset of action, with continued improvement over the course of the clinical trial.

For the ACR 50, there's a somewhat slower onset, but the response builds over time and is increasing at the end of the clinical trial, for both active treatments.

And a similar result is seen with the ACR 70.

As expected, tocilizumab has a dramatic effect on acute phase reactants through its interaction on IL-6, and one can see that demonstrated from the 822 trial, with a rather dramatic effect on the CRP in both active treatments after the first dose.

However, it is only the 8 mg/kg

dose that keeps the CRP close to normal throughout the entire clinical trial period. The 4 mg dose has a more intermediate value and does not fully normalize the CRP. A similar result is seen with the erythrocyte sedimentation rate.

However, it is not just this dramatic response on CRP that drives the patient's clinical response. If one looks at the core parameters in the ACR response criteria, one can see that all the active treatments were statistically better than placebo in all of the core variables.

If we look at those patients on a pooled basis who achieved a DAS28 less than or equal to 3.2, or a DAS28 less than 2.6, again, both active treatments achieved this clinical endpoint.

As rheumatologists, we know that patient-reported outcomes are becoming increasingly important both to us and to our patients, and we looked at several of these

in the clinical development program for tocilizumab. Depicted on this slide is the mental component score and the physical component score from the SF-36, and both active treatments were statistically better than placebo. And both active treatments met the MCID for this particular endpoint.

If we look at the HAQ, the patients started with a baseline HAQ of around 1.6, and both active treatments ended around 1 by the end of the clinical trial. And about 60 percent of the patients at the end of the trial had an improvement of greater than or equal to .3 by week 24.

Controlling rheumatoid arthritis for a six-month period, while it's a laudable goal, we know that rheumatoid arthritis is a lifelong disease. So control of the disease over a longer period of time is what is expected. So if we look at the responses of those patients who entered the long-term extension to these clinical trials, one can

see that those that were on the 8 mg/kg maintained their ACR 50 and ACR 70 responses during the long-term extension, and those patients who started on 4 mg/kg and placebo had increases in their ACR 50 and ACR 70 during the long-term extensions.

I will now show you the recently available one-year data from the 823 trial, and again, I caution you that this is data that has recently been unblinded, and the FDA has not yet had a chance to fully review this data.

If we look at the disposition of these patients at the one-year timepoint, about 85 percent of these patients completed the clinical trial on their assigned therapies. About 50 percent of the patients completed the clinical trial via the escape mechanism on placebo, whereas 24 percent and 15 percent of patients completed the clinical trials via the escape on the 4 mg and 8 mg, respectively.

Again, as expected, more patients discontinued for adverse events in the active treatment arm, while more patients discontinued for lack of efficacy on the placebo arm.

If we look at the ACR 20, 50, and 70 from the six-month timepoint as a reminder, one can see that the ACR 20 was significant for both active treatments, and the ACR 50 was significant for the 8 mg/kg. And if we look then at the one-year data, one can see that the ACR 20 responses were maintained through the second six months of the clinical trial, while there were increases for both the active treatment arms in the ACR 50 and ACR 70 during the second six months of the trial.

If we look at those patients who achieved a DAS28 of less than 2.6, again, one can see at week 24, those patients who were on 4 mg/kg and 8 mg/kg, and then look at one year; there continues to be an increase in

the patients achieving this endpoint, with almost 50 percent of the patients on the 8 mg/kg dose achieving this endpoint at one year.

If one looks at the radiographic progression over the course of this trial, using the Genant modified total Sharp score, once can see that the placebo progressed at a rate of about 1.13 Sharp units per year. On the 4 mg/kg dose, there was about a 70 percent reduction in radiographic progression at one year, and at the 8 mg/kg dose, there was an approximately 75 percent reduction in radiographic progression at one year. Similar results were seen in the erosion score and the joint space narrowing score.

We'll now turn our attention to those patients who used tocilizumab in combination with DMARDs who had had an inadequate response to previous anti-TNF therapy.

This was looked at in the 062 trial, and the trial design is depicted here. The patients were screened, their methotrexate was continued, their other DMARDs were discontinued, and they were randomized in a 1:1:1 fashion to receive either tocilizumab 8 mg, 4 mg, or placebo. It was again a six-month study with a primary endpoint of an ACR 20, and at the end of that period, they also were eligible to enter open-label extension of tocilizumab 8 mg/kg.

The baseline characteristics are depicted here and are similar across all treatment groups, and it's similar to other clinical trials that have looked at this patient population. The mean age was around 54. The mean duration of disease activity was around 12 years. They all had significant baseline activity, as shown by a mean DAS28 score of 6.8.

Again, they had 20 and 30 swollen and tender joints, respectively. About

50 percent of these patients again were on background oral corticosteroids, and the mean dose of methotrexate in these clinical studies was about 16 mg per week.

About 50 percent of the patients entered this clinical trial having failed one anti-TNF therapy. The other 50 percent had failed at least two anti-TNFs. And the majority, over 80 percent of these patients, had failed their anti-TNF because of lack of efficacy.

If we look at the disposition at week 24, 80 percent of the patients completed the clinical trial, 41 percent completed the clinical trial via the escape mechanism on the placebo arm, while 19 and 11 percent of the patients completed the clinical trial via escape for the 4 mg and 8 mg, respectively.

The number of patients who discontinued for adverse events was equal and balanced across all treatment groups, and those patients who failed for lack of

efficacy were more on the placebo arm than on the active treatment arm.

If we look at the response to the ACR scores in this patient population, both active treatments were significant for the primary endpoint of ACR 20. However, for ACR 50 and ACR 70, only the 8 mg/kg dose was statistically different than placebo.

If one looks at the response having failed one, two, or three anti-TNFs, one can clearly see that there's a drop-off in response, primarily to ACR 50 and 70, if the patient had failed at least three anti-TNFs.

If we look at those patients who achieved a DAS28 of less than or equal to 3.2, or a DAS28 less than 2.6, again, it was only the 8 mg/kg dose that achieved statistical significance on this endpoint.

And now I'd like to turn our attention to the use of tocilizumab as monotherapy. This was done in the 824 trial, where only the 8 mg/kg dose of tocilizumab

was tested. The control group was methotrexate in a titrating fashion. Zero to three weeks, they received 7.5 mg per week; for weeks four through seven, they received 15 mg per week; and in weeks eight through 24, they received 20 mg per week.

This again was a six-month clinical trial with an ACR 20 as the endpoint. The patient population studied was those patients who were naïve to methotrexate or who had not previously failed methotrexate for efficacy or safety reasons.

The clinical trial design is depicted here. The patients were randomized to receive either tocilizumab 8 mg/kg, a titrating dose of methotrexate as mentioned previously. And also to serve as an internal control, an eight-week placebo arm was added to the clinical trial. This placebo control portion was done in the United States, Canada, and Israel.

After the eight weeks, these

patients were then rolled over to double-blind tocilizumab at 8 mg/kg. Again, the primary endpoint was the ACR 20 at six months, and at the end of the clinical trial, these patients were eligible to enter open-label tocilizumab at 8 mg/kg.

The baseline characteristics are depicted here. Again, the mean duration of disease activity was approximately 6.4 years; however, over 40 percent of these patients had a disease activity duration of less than two years. They all had significant background disease activity, as manifested by a mean DAS28 of 6.8. Again, 20 and 30 swollen and tender joints were seen.

About 50 percent of these patients were on background oral corticosteroids, and three-quarters of them were on background NSAIDs. Two-thirds of the patients were truly methotrexate-naïve, and between 40 and 45 percent of the patients were truly DMARD-naïve.

If we look at the disposition at week 24, over 90 percent of the patients completed the clinical trial, with 11 patients completing via the escape mechanism in the methotrexate arm, and seven patients completing via the escape in the tocilizumab arm. More patients discontinued the clinical trial for adverse events and lack of efficacy in the methotrexate than in the tocilizumab monotherapy arm.

This trial was set up as a non-inferiority trial, with the placebo serving as an internal control. And as one can see, the 95 percent confidence intervals with a weighted difference between either methotrexate or tocilizumab do not cross zero. So both tocilizumab and methotrexate were different than placebo and were effective therapy.

As I said, this was set up as a non-inferiority trial, with a margin of 12 percent. Because of this, the primary

analysis was done on a per-protocol population, and since the 95 percent confidence interval of the weighted difference between tocilizumab and methotrexate did not break the non-inferiority boundary, we can say that tocilizumab in monotherapy at 8 mg/kg was non-inferior to methotrexate monotherapy.

There was a pre-specified protocol stipulation that if the non-inferiority margin was not breached, then a testing for superiority was provided, according to ICH guidelines. And if we look at the ACR 20, the ACR 50, and the ACR 70, more patients on the tocilizumab monotherapy arm achieved this endpoint than those on the methotrexate arm, and this was statistically significant.

Also, if you look at those patients who achieved a DAS28 less than or equal to 3.2, or a DAS28 less than 2.6, more patients on the tocilizumab monotherapy achieved this endpoint than those patients on methotrexate.

So in conclusion, the primary endpoint was met in all five double-blind placebo-controlled trials.

Tocilizumab is effective as monotherapy or in combination with DMARDs. Tocilizumab has been shown to alleviate the signs and symptoms of RA across a wide range of RA patients, from early RA through DMARD inadequate responders to those patients who have had an inadequate response to anti-TNF therapy.

There were consistent and robust effects on all endpoints, particularly the ACR 50, 70, and a DAS28 of less than 2.6. There was a rapid response within two weeks, and continued improvement with up to two years. And improvement in patients' quality of life and physical functioning was also seen.

Tocilizumab in combination with DMARDs in patients who have had an inadequate response to anti-TNF therapy, the 8 mg/kg

dose every four weeks was consistently more effective than the 4 mg dose.

And in patients with an inadequate response to DMARDs, both the 4 and 8 mg doses were effective; however, the 8 mg dose was consistently more efficacious than the 4 mg dose. However, in a certain subset of population in a DMARD-IR group, a dose of 4 mg may be considered as a starting dose, followed by adjustment to 8 mg/kg based upon that patient's clinical response.

And in monotherapy, tocilizumab is effective at a dose of 8 mg/kg in reducing the signs and symptoms in a wide range of RA patients.

Thank you.

With that, I'd like to turn it over to Dr. Joel Krasnow, who will discuss the safety.

DR. KRASNOW: Thank you. Good morning. I will be presenting the safety data this morning. The areas which we will start

with is, first, we will define the safety populations. Then we will describe the exposure by dose. We will be providing an overview of the safety profile, and then focusing the majority of our time on events of special interest. I will then turn it over to Dr. Van der Auwera, who will discuss our pharmacovigilance plan.

The key safety populations comprising the safety database are listed here. They consist of the six-month controlled study population, all patients exposed to tocilizumab during the Phase III clinical development program, and in portions of the presentation, we'll be citing the Chugai data from Japan, where clinically relevant, for the RA population.

The controlled studies include five pivotal trials, as described by Dr. Bahrt, up until the time of escape. At the time of the escape, all patients know that they will be receiving tocilizumab, and therefore are

unblinded and are censored at this time. We also report events that occur up to three months from the last dose of study drug.

The all patients exposed to TCZ, representing all patients in the Phase III program, consists of the controlled clinical trials as described above, those patients entering escape, those patients in the transition phase from the monotherapy trial, and also the patients from the open-label long-term extensions.

Because of the fact that we are pooling here patients from controlled clinical trials and open-label trials, the data will be presented in rates per 100 patient years. The number of patients who were exposed to tocilizumab for the 8 mg, control, and 4 mg doses are shown here at three and six-monthly intervals.

When we look at exposure beyond 12 months, we note that the majority of the exposure is on 8 mg, with some exposure in

the control arm representing the transition-phase patients.

I'd like to provide an overview of the adverse events, and also describe the way in which the data will be displayed throughout the presentation. The monotherapy trial will be represented on the left-hand side of each slide. These patients have different patient characteristics, and also are at a different risk for various events such as severe infections, and therefore will be presented separately from the DMARD inadequate responder population.

When we look here, we see a 2 percent increase in adverse events and a 1 percent increase in severe adverse events for patients exposed to tocilizumab, compared to those receiving methotrexate. With respect to AEs leading to withdrawal and AEs leading to dose modification, we see a higher percentage of patients experiencing these events on the methotrexate arm. If we then

look at patients who are on a background of DMARD and also received 4 and 8 mg of tocilizumab, we note that the incidence of events between the two tocilizumab arms is quite similar, and distinct from that of the patients who are receiving DMARD alone. Deaths are noted in all patient groups, with the exception of the 4 mg tocilizumab arm.

If we then look at adverse events that are occurring in greater than 2 percent of the population, we have organized them in descending order according to the incidence in the tocilizumab monotherapy arm. We have also included all events that are occurring more frequently in the tocilizumab arm compared to a comparator; the comparator may either be methotrexate in the monotherapy, but for instance, in this example, we see that increased transaminases are occurring more frequently in the methotrexate arm.

However, if we then look across, we find that compared to the DMARD combination

therapy, they are occurring at a higher incidence in patients receiving both DMARD and tocilizumab.

For serious adverse events, we have included all serious adverse events that are occurring in three or more patients receiving tocilizumab, whether the tocilizumab is in monotherapy or combination therapy. The most common adverse events noted as a class are those of infections, with the most common being pneumonia, followed by cellulitis, herpes zoster, sepsis, and gastroenteritis.

From a cardiovascular perspective, the events observed include myocardial infarction and acute coronary syndrome and carotid artery stenosis. We will be discussing cardiovascular events later on in the presentation. Additional events occurring in greater than or equal to three patients include falls, femur fractures, pulmonary embolism, back pain, and neutropenia.

During the controlled six-month studies, the leading causes of death were cardiac and vascular and infection. Five deaths occurred in the control arms and in the tocilizumab arms. Due to the relatively greater numbers of patients receiving tocilizumab relative to the comparator arms, the overall rate, when adjusted for patient years of exposure, is 0.4 in the tocilizumab and 0.8 in the control.

When we look at all TCZ-exposed during the Phase III program, which is presented in the safety update of October 1st of 2007, we note that the leading causes of death continue to be cardiac and vascular and infectious in etiology. We note that there are no deaths in the 4 mg arm, and the rate of death that we observed in the tocilizumab and the control arms are comparable, and the Chugai rate is listed here for reference.

I'd like to now focus on different areas and events that are of keen interest.

The reason for the selection of these events is twofold: Firstly, some of these events are events that have been reported with other biological therapies such as demyelination and malignancies; others of these events are events that are of clinical importance in the area of rheumatoid arthritis, and also that may be impacted by the Interleukin-6 mechanism of action. Our goal in discussing these areas is to present the data and then present a way for minimizing risk to the patient.

We start with infections, which represent the most common serious adverse event which patients exposed to tocilizumab will experience. About one out of every three patients will experience an infection. The withdrawal due to infection during the controlled clinical trials was approximately 1 percent across all groups. The rate of serious infection for the patients in monotherapy receiving methotrexate was 1.5

per hundred patient years, and for those receiving tocilizumab, it was 3.6. The DMARD-IR population have slightly higher rates of serious infection, with 3.9 being observed in the DMARD alone, 4.4 in the DMARD plus 4 mg, and 5.3 in the DMARD plus 8 mg group.

This slide illustrates the all TCZ-exposed, or the entire Phase III population, and looks at the rate of infection per hundred patient years and the number of deaths and rate of deaths due to infection. When we look at the rate of death due to infection, it ranges across all treatment groups from 0.10 to 0.15.

Looking at the rates of serious infection at six-monthly intervals, we note that the rate of serious infection is consistent over time. When we get beyond two years, the exposure is limited, and therefore there's a wide confidence interval for this value.

Opportunistic infections have been observed with tocilizumab. There have not been any opportunistic infections reported in patients in the control group. Specific opportunistic infections that have been reported include mycobacterium avium intracellulare and tuberculosis.

For tuberculosis, there have been two cases reported in the 8 mg group, for a total of two cases in the entire Roche program. Within the Chugai experience in Japan, there have been three cases of tuberculosis reported. Other opportunistic infections include pneumocystis carinii pneumonia, one case of Epstein-Barr virus reactivation and pulmonary aspergillosis, both in the Chugai data set, and one case of candid osteomyelitis.

With respect to herpes infections, the key point is the last line, which indicates those patients requiring hospitalization. The reason for

hospitalization in these patients was the need to administer acyclovir intravenously, and this is occurring only in the tocilizumab and not in the control patients.

In summary, the rates of serious infections, including opportunistic infections, are elevated over control and do not increase over time.

For 8 mg, rates of serious infections are consistent with those observed with anti-TNFs. In order to decrease the likelihood of experiencing an infection that becomes serious, tocilizumab treatment should not be initiated in patients with active infection. Tocilizumab should be interrupted if a patient develops a serious infection, or an infection that could become serious, until the infection is controlled.

Despite only seeing two cases of tuberculosis in the Roche clinical trial program, we are recommending that tuberculosis screening be performed prior to

initiating tocilizumab, and if the patient does test positive, that treatment be initiated according to clinical practice guidelines. In addition, at this time, we are also recommending that live attenuated vaccines not be given while patients are on tocilizumab.

I'd like to now move on to one of the pharmacodynamic characteristics of IL-6 and its inhibition by tocilizumab. With neutrophils, what we see is a dose-dependent decrease in neutrophil count that occurs shortly after initiation of treatment. With the 8 mg, this decrease is relatively consistent. With the 4 mg dose, what we see is a greater recovery towards the baseline levels that are occurring as we approximate to the nadir of the dosing interval at approximately four weeks.

While this figure shows the mean changes in neutrophil count, we would also like to look at the number of patients who

may fall to levels below the lower limit of normal.

What we see here are the CTC grades from just below the lower limit of normal to those that are going to below 1,000 and below 500. What we note is that 3 percent of patients on tocilizumab 8 mg, and 1 percent on 4 mg, are falling to levels that are below 1000 absolute neutrophils. There were eight patients who went below 500, and these were discontinued.

We also note that there are no serious infections observed in that cohort of approximately 75 patients that have Grade 3 and Grade 4 neutropenia. There were five non-serious infections seen in Grade 3 or 4 neutropenia: Two bronchitis events, one sinusitis, one pharyngitis, and one conjunctivitis.

Despite the lack of serious infections in patients with an ANC below 1,000, we will be advising that we should

maintain absolute neutrophils counts above that threshold.

Our plan and recommendations are as follows. First, that tocilizumab should not be initiated in patients with neutrophil counts above 2000 at the time of initial presentation; that neutrophils be monitored at four to eight weeks after the first infusion in all patients; and that laboratory parameters be repeated as indicated.

For absolute neutrophil counts above 1,000, the dose should be maintained of tocilizumab. Should the neutrophil count fall below 1,000 and be above 500, we recommend interruption, and then when the ANC is above 1,000, resuming the dose at 4 mg and returning to 8 mg as clinically appropriate. For patients whose ANC is below 500, we are recommending discontinuation of tocilizumab.

Gastrointestinal perforations were noted in our clinical development program. I will be providing you an overview of the

cases of gastrointestinal perforations.

Within the controlled six-month clinical trials, there was one perforation noted within the duodenum and two diverticular perforations noted. These occurred on 8 mg/kg. There were no gastrointestinal perforations noted on the control.

As a consequence of this imbalance, quarterly review of these cases and reporting of these cases was initiated.

We are therefore reporting all gastrointestinal perforations through March 31st of this year. If we focus for a moment on the Roche cases, we note that there are three upper GI perforations, and for lower GI perforations, we note one on the 4 mg dose, and this has occurred in the 823 study and was not part of the original submission. But we are giving a more up-to-date view. There are nine lower GI perforations on the 8 mg, for a total of 10

lower GI perforations. When we look at the rate per thousand patient years of exposure, this provides us with a rate of 1.5 or 1-1/2 per thousand patient years. If we then look at the Chugai experience for upper GIs, they have also observed three upper GI perforations, and they have observed four lower GI perforations.

In order to compare the rates observed in these clinical trials, we have looked to the literature. The VIGOR study looked at RA patients randomized to rofecoxib or Naproxen, and they reported a rate of upper GI perforation of 1.3 per thousand patient years. The rates for the Roche and Chugai studies are listed below.

For lower intestinal perforations, we were unable to find any rates in the literature for RA patient population. Therefore, we went to claims databases, and I present to you here the United Health Care claims database. This represents over 30,000

patient years of experience in the RA population, and the rates observed here are 0.9 for the entire cohort of RA patients, with increases in those exposed to methotrexate, a rate of 1.3 for those exposed to anti-TNF, and a rate of 3.9 per thousand patient years for those on corticosteroids.

In summary, the rate of GI perforations at 8 mg is elevated over control, but is similar to the RA background observed in RA databases. Tocilizumab should be used with caution in patients with a history of diverticulitis. GI mucosal protection is advised for patients receiving NSAIDs and corticosteroids.

Patient education should include the potential risk for GI perforation, information on the signs and symptoms of diverticulitis, and the prompt reporting of symptoms to the health care provider. Patients presenting with abdominal symptoms should be promptly evaluated, with

appropriate referral as needed.

Demyelination has been reported in patients receiving TNF inhibitors. The pattern and time course is similar to that observed in multiple sclerosis. This is a diagnosis of exclusion supported by the presence of white matter lesions on the MRI.

Listed here are patients that represent potential cases of demyelination. These three patients all had white matter lesions noted on the MRI. The first two patients are patients who have a history of significant vascular disease. The third patient presented with syncope. She's a 56-year-old female, and has been followed for a further one year since the time of the reporting of this initial event.

Over the course of this year, this patient has had no neurological symptoms. Also presented here are three additional cases. Optic neuritis is a case that has been reported to ultimately go on to

subsequent demyelination. It is also commonly seen in patients with multiple sclerosis. It is also commonly seen in patients with autoimmune diseases, and other causes include vasculitis.

For this patient, the MRI revealed no demyelination. The next patient, with occipital neuropathy, had her symptoms resolved shortly following the initial diagnosis. The last patient, with chronic radiculoneuropathy, presented with a history of paresthesia, peroneal nerve palsy, and carpal tunnel syndrome even prior to the trial.

She was initially randomized to the placebo arm, and the disease progressed while on the placebo arm, with progressive weakness and weight loss. She then was transferred to the extension studies, where she received tocilizumab, and unfortunately, the patient's condition continued to progress.

In summary, all cases of potential

demyelination reported to date also have other causes for the clinical findings or have improved spontaneously. Should new neurological symptoms develop, or progression of an existing neurological condition occur, patients should be evaluated and treated as appropriate. If demyelination is suspected, tocilizumab should be discontinued.

In rheumatoid arthritis, the rate of malignancy is elevated. I will provide an overview of the cases of malignancy observed to date within the clinical trial program.

First, in the controlled clinical trials, if we focus our attention at the overall rate, we see similar overall rates across the treatment groups reported during the initial six-month studies.

Looking at all patients exposed during the entire Phase III clinical program, we see heterogeneous tumor types. And then if we focus also on the overall rates seen, we see comparable rates across all of the

treatment groups.

In summary, although to date small numbers of cases have been reported and the duration of follow-up is relatively short, we are committed to further pharmacovigilance, which is planned. Caution should be exercised in patients with a history of malignancy, as immunosuppression may affect host defenses against malignancies. All patients receiving tocilizumab should be screened according to clinical guidelines.

Cardiovascular events are a leading cause of morbidity and mortality in RA. Therefore, it is important to discuss factors that may impact cardiovascular events.

And I'd like to start with the lipids. Following initiation of tocilizumab, there is an increase in LDL, and in addition, an increase in HDL of approximately 10 percent. At baseline, across all treatment groups, the baseline LDL level was approximately 115 mg/dL.

If we focus on the 4 mg group, two weeks following infusion, the level is 133, and then what we see is a decrease between week two and week four, with the average level four weeks following infusion at 127.

The thresholds shown on this slide of 130 and 160 mg/dL are commonly used thresholds for basing treatment decisions in patients with cardiovascular disease. If we focus here on the monotherapy, we note that approximately 11 percent more patients will shift from a level below 130 to a level above 130 with initiation of tocilizumab treatment, and a similar percentage of patients will shift from below 160 to above 160. And the data are numerically different, but the pattern is very similar for the combination therapy.

Four patients who received the statin while in the clinical trial. So this is a subgroup of patients who received the statin. They started off with an LDL of 135.

Following initiation of tocilizumab, the LDL went to 169, and then following initiation of therapy, the LDL was reduced as expected, the mean level being 128 mg/dL.

Looking at other atherogenic indices, and commonly used indexes used to measure cardiovascular risk, we show here the LDL:HDL ratio and the ApoB:ApoA1 ratio. Again, if we focus on the 4 mg group, we see a .2 increase in the LDL:HDL ratio, and relatively little change in the ApoB:ApoA1 ratio.

LDL increases with tocilizumab treatment. The impact is such that 11 to 23 percent of patients will shift ATP III categories. A lipid panel should be obtained four to eight weeks following initiation of tocilizumab, and then lipid levels should be maintained within target ranges and managed with lipid-lowering agents if clinically appropriate.

Hypertension is an established risk

factor for cardiovascular disease. If we focus at the combination therapy patients, we see approximately a 2 percent difference in the incidence of adverse events of hypertension between the DMARD and the DMARD plus tocilizumab arms. If we then look at the breakdown, we see that approximately one-third of the adverse events of hypertension are occurring during or right around the time of the infusion, another one-third in patients with a history of hypertension, and the last third in patients without a history of hypertension.

When we look at systolic and diastolic blood pressures and we look at the change from baseline, we see no increase in blood pressure in any of the groups treated with tocilizumab, either in monotherapy or in combination therapy.

When we then look over time -- and this is through two years of therapy in patients on our long-term extension

studies -- we see that the blood pressures are stable through two years of therapy.

Moving to the clinical events, this represents the clinical cardiovascular events throughout the entire Phase III program. This represents the serious cardiac events. If we look at the total, the total rates are 0.92, 1.2, and 1.27, respectively, for the 4, 8 mg, and control populations. Categorizing the type of severe cardiac event, from myocardial infarctions and acute coronary symptoms, .46, .32, and .64. The rates are also shown for ischemic heart disease, arrhythmia, cardiac failure, and cardio-respiratory arrest.

If we look specifically at the rates of myocardial infarction and stroke, we see that for both of these clinical events, the rates are stable with increasing doses of tocilizumab.

If we then look at the rate of these events over time, we see that the rate

of these events over time is not increasing.

In summary, there is no increase in mean systolic or diastolic blood pressure in patients receiving tocilizumab. The rate of CV events is stable with prolonged exposure to tocilizumab and comparable to control. Tocilizumab decreases inflammation and increases LDL. We recognize that long-term follow-up is required to more accurately estimate the effect of tocilizumab on cardiovascular events.

Optimal management of cardiovascular disease includes management of all cardiovascular risk factors. For this reason, we recommend that a lipid panel be obtained following four to eight weeks of tocilizumab therapy, and that patients be managed according to guidelines; also that blood pressure be monitored, and routinely and optimally managed. Physician and patient education programs regarding cardiovascular risk factors and the impact of tocilizumab

therapy on those factors will be initiated.

Patients will be followed for the occurrence of cardiovascular events while on tocilizumab for a minimum of five years in our extension studies, with additional work ongoing in the registries.

I'd like to move to another pharmacodynamic wild value that is altered by the administration of tocilizumab.

Patients who entered the trials were very close to the upper limit of normal for their platelet count. Upon initiation of therapy, the platelet count is reduced in a dose-dependent fashion in both the 4 and the 8 mg group, and these values are stable over time.

The number of patients who are experiencing Grade 3 and 4 events is shown here, and the events that have occurred in this patient population include two events of epistaxis, one of hemoptysis, and one hemorrhaging stomatitis reported in this

patient population.

Therefore, tocilizumab should not be initiated in patients with platelet counts below 100,000, and they should be monitored four to eight weeks following infusion and repeated as clinically necessary. Should the platelets fall to between 50,000 and 100,000, the tocilizumab should be interrupted, and then when the platelet count is over 100,000, it should be resumed at a dose of 4 mg, returning to 8 mg as clinically appropriate. For patients with platelet counts below 50,000, we recommend discontinuation.

I'd like to transition now to discuss liver enzyme changes that are occurring.

This represents the change in ALT that is occurring in the monotherapy trials with both the methotrexate and the 8 mg/kg of tocilizumab.

If we then look at the combination therapy, what we see is dose-dependent

increases in the 4 and the 8 mg group with respect to ALT. If we look then at the percentage of patients that are crossing various thresholds for hepatic transaminases, I'd like to focus for now on the groups that are going above three to five times the upper limit of normal, and above five times the upper limit of normal.

And what we note for the monotherapy trials is that the numbers of incidents are similar between the tocilizumab and the methotrexate for ALT and for AST. When we look at the percentage of patients who have the doses held, it's 8 to 10 percent, and this is in part because it includes methotrexate dose being held, and as Dr. Bahrt has shown, there was a dose escalation of methotrexate that occurred as part of the clinical protocol.

If we then look at the combination therapy, we see that more patients receiving tocilizumab are having ALT increases to above

three times the upper limit of normal. Again, the percentage of patients who had doses held was 3 percent, and the percent that required discontinuation was 1 percent.

There were two specific cases that we'd like to go into in some detail here, the reasoning being that these are patients who had concurrent elevation of their transaminases to above three times the upper limit of normal, with concurrent elevation of the bilirubin to twice the upper limit of normal.

The first is a 31-year-old female who presented with biliary colic, and the transaminase and bilirubin are shown here. Once the patient passed a gallstone, these laboratory parameters returned to within normal limits. The second patient is represented here as a 57-year-old female.

She initially received tocilizumab in the monotherapy trial, with tocilizumab alone, and there were no elevations noted in

hepatic transaminases. She then moved on into the extension study and was initiated at a dose of 20 mg of methotrexate weekly.

Following this, the transaminases were increased as shown, and the bilirubin was increased as well. If we look at the fractionation of the bilirubin, we find very little direct, but that the majority of the bilirubin is indirect, conferring a diagnosis of Gilbert's Syndrome to this patient.

If we then look in more detail at the more common phenomenon of hepatic transaminase elevation that is within the one to three times the upper limit of normal, we see that in the monotherapy trial, it is occurring at similar frequencies. Within the combination therapy, we do see an increased frequency of this event occurring with the combination of DMARD plus tocilizumab.

If we then look and characterize the pattern, what we see for the monotherapy is that approximately 14 percent of these

cases are occurring at a single timepoint, and by definition, not recurring. Five percent with consecutive recurrences, and again, approximately 13 percent with non-consecutive elevations, meaning that the value went up, came down, and at a subsequent time went to above normal. Most of the increases to above the upper limit of normal are usually between 1 and 1.5 times the upper limit of normal.

If we then look at the DMARD combination patients, we also note similar rates for single timepoint and for two consecutive values. But what we do see is increased frequency of non-consecutive elevations occurring in the DMARD combination therapy patients.

In summary, most ALT and AST elevations were transient and returned to normal without dose adjustment or treatment discontinuation. Elevated transaminases were not associated with reduced liver function in

over 4000 patient years of exposure. Also, there were no serious adverse events associated with any of the transaminase changes observed in the clinical trials.

Recommendations: First, that tocilizumab should not be initiated in patients with ALT or AST greater than 1.5 times the upper limit or normal, or in patients with other evidence of liver disease. ALT and AST should be monitored four to eight weeks after the first infusion in all patients, and the laboratory assessments repeated as clinically indicated.

For patients with values falling between one and three times the upper limit of normal, the data I've shown indicate that for a single elevation, no intervention needs to occur. However, should the elevation be recurrent or persistent, then we would recommend to first modify the concomitant DMARDs, and for persistent increases despite modification of the DMARDs, then to consider

modifying the tocilizumab in order to normalize ALT and AST levels. For elevations greater than three times the upper limit of normal, we are recommending interruption of tocilizumab until hepatic transaminases fall below three times the upper limit of normal, and then to dose reduce to 4 mg/kg or resume the full dose. For persistent or recurrent increases, we recommend discontinuation. And for increases above five times the upper limit of normal, we recommend discontinuation.

A common concern with any biologic administered through the intravenous route is an infusion reaction.

The anaphylactic reactions and hypersensitivity were reported on both doses of tocilizumab in monotherapy and combination therapy, but not in any of the control patients. Infusion reactions were not correlated with the development of anti-tocilizumab antibodies.

For all patients exposed to TCZ population, similar findings are noted, with three anaphylactic reactions occurring in the 4 mg and three occurring in the 8 mg group.

In summary, infusion reactions and the development of anti-TCZ antibodies were rare. There were six cases of anaphylaxis, three each on the 4 and the 8 mg dose. The infusion setting should be staffed with experienced personnel and appropriate medications and equipment to manage anaphylactic reactions.

The overall safety recommendations are as follows. Patients and their health care professionals need to be vigilant for early signs of infection and diverticulitis. Tocilizumab should be withheld if infection is suspected. Laboratory monitoring of hepatic transaminases, neutrophils, and platelets should be performed four to eight weeks following initiation of therapy.

Lipids should also be assessed four

to eight weeks following initiation of therapy to determine if lipid-lowering agents are appropriate. Health care providers administering tocilizumab should be alert for signs of anaphylaxis, and should be prepared to intervene as needed. Accurate assessment of malignancy rates and cardiovascular events will require ongoing surveillance.

At this juncture, I'd like to ask Dr. Van der Auwera to discuss our pharmacovigilance plans.

DR. VAN DER AUWERA: Thank you very much. Well, good morning. I would like to review quickly for you the way we would like to propose an integrated risk management plan once tocilizumab is part of the normal armamentarium of rheumatologists in this country.

The first aspect of risk mitigation is labeling, and you heard a lot, as presented by Dr. Krasnow, on how we are proposing to manage. Patient package inserts will contain appropriate information. There

will be a program to educate patients, nurses, and physicians. And that's particularly important and is shown to be effective with previous biologics that have been put on the market.

From a pharmacovigilance perspective, we intend to put in place large cohorts of patients treated with tocilizumab in known and respectable RA and biologic registries, both in the U.S. and in Europe. There will be enhanced pharmacovigilance for specific events; in particular, a guided questionnaire that will allow us to better understand and have richer information about events of interests that I will be more specific about in the next slide.

We will participate through pregnancy registry and make sure that patients who are reporting pregnancy during treatment of tocilizumab are well-followed and information captured. We will continue to analyze claims databases as an additional

approach to understand and ascertain certain rates of rare events. Furthermore, long-term safety studies will be continued, specifically to ascertain what are potential elements of risk that are time-dependent.

From a clinical perspective, there are expected risks that are observed in rheumatoid arthritis patients, especially when they are treated with potent immunomodulating agents, including tocilizumab. Anaphylaxis, serious and opportunistic infections, malignancy, and demyelinating disorders are areas of specific interest.

Newly recognized risks are gastrointestinal perforations, which we considered as a signal that has been observed in our database. Nevertheless, they seem to be a background rate that is not well-ascertained in rheumatoid arthritis patients, but also when they are treated with various treatments, including methotrexate,

corticosteroids, NSAIDs, and biological agents. We will also implement risk mitigation strategies, and you heard about labeling.

Patient information, education of patients, physicians, and nurses are all very important. There has been a certain number of lab parameters that are pharmacodynamic elements linked to the mode of action of tocilizumab; namely, impact on the liver enzymes, neutrophils with neutropenia seen occasionally, decrease in platelets, and elevation of lipids. The risk mitigation strategy that we are proposing in the label constitutes in monitoring four to eight weeks after initiation of treatment, and thereafter as required by appropriate medical judgment.

Dose modification and dose interruption are recommended for liver enzyme elevation, neutrophils, and platelets. For lipids, there is clear guidance in the label for initiation of treatment according to

existing guidelines with lipid-lowering agents.

More specifically, we would like to initiate tocilizumab cohorts in existing biologic and rheumatoid arthritis registries. These will provide control population with patients that are treated with other therapies, biologics or nonbiologics. These will be implemented in the U.S. registries and E.U. registries for five-year follow-up.

The target number of patient years that we intend is 25,000 patients, although this needs to be discussed more specifically with the agency later on. Should we have a target of 25,000 patient years, we would be able to detect a risk ratio of 1.4 for MI and other risks of interest, like stroke or serious infections.

With this type of sample size, 25,000 patient years, we would have the ability to detect a risk ratio of 2 for GI perforation. Interim and final summary

reports are planned, and we will have regular discussion with an independent group of experts representing various specialties of medicine and a statistician. And we will also participate to existing pregnancy registries.

We'll also continue to use claims database analysis, as they have shown their value, especially in understanding certain elements that are easily identified by ICD-9 codes. They have adequate sensitivity and specificity for rare events, and in particular for cardiovascular events, strokes, also the initiation of treatment like statin as a surrogate for an elevation of LDL that might be associated with tocilizumab.

Likewise, procedures like liver biopsies are easily recognized in claims databases, and can be followed as a surrogate for potentially important liver adverse events.

We will continue to keep patients that were enrolled in the clinical program for up to five years or longer, and this constitutes an initial cohort of 2,500 patients that will allow us to perhaps examine what is the evolution of risks during longer treatment with tocilizumab. In summary, we are committed to continue to follow up the risks associated with tocilizumab use and the efficiency of the mitigation activities that we are proposing.

We believe that we have a good understanding of the data obtained so far in a pretty large development program. We have clearly identified the need for additional data, especially in areas of interest and rare events, and how we intend to acquire these more data.

And we have a comprehensive strategy to mitigate recognized and potential risks.

Dr. Bahrt is going to summarize our

presentation. Thank you.

DR. BAHRT: So in summary, as rheumatologists, we know that rheumatoid arthritis is a multifactorial disease with a common clinical phenotype that's reached by a variety of different routes. We know that new therapies with novel mechanisms and actions are still needed, since many patients respond sub-optimally to currently approved therapies, or lose their effect over time. As you heard previously, remissions are still rare. ACR 70 responses are still infrequent.

And many times, the best we can do is get 50 percent of our patients 50 percent better. And again, since rheumatoid arthritis is a lifelong disease, many patients who initially respond, even having good responses to the current therapies, lose that response over time. So tocilizumab offers a new approach to the management of this disease.

In a comprehensive clinical

development program, tocilizumab demonstrated reliable and consistent efficacy in monotherapy or in combination with DMARDs in a range of RA patients. Improvement was seen in the patients' quality of life and physical functioning. Effective control of inflammation throughout the entire dosing period was also seen. And the clinical benefit was sustained over the two years of long-term extension follow-up.

In an anti-TNF inadequate responder population, tocilizumab at 8 mg/kg was consistently more efficacious than the 4 mg/kg dose. In a DMARD IR population, although both doses were effective, 8 mg/kg every four weeks was more efficacious than the 4 mg/kg in reducing signs and symptoms in a majority of patients.

However, a 4 mg/kg dose may be considered, followed by an adjustment to 8 mg/kg based upon the patient's clinical response and a rheumatologist's evaluation of

that individual patient's benefit risk. For example, the young patient who comes to you with disease that is rapidly progressing and is otherwise healthy may be an ideal candidate for 8 mg/kg, with reduction or modification of the dose down to 4 should safety issues intervene.

For those patients who are more fragile from a safety standpoint, a dose of 4 mg may be the appropriate starting dose based upon your determination of benefit risk for that patient, and then adjustment to the 8 mg/kg dose as required for clinical benefit.

In patients where DMARDs were not considered appropriate, tocilizumab monotherapy at 8 mg/kg provides a clinical response that is superior to methotrexate.

Balanced against this, we have seen in a comprehensive development program tocilizumab monotherapy and in combination with DMARDs has demonstrated a

well-characterized adverse event profile; a risk of serious infection that is comparable to other biologics; a risk of malignancy and cardiovascular events that is similar to the background rate seen in an RA population; a rate of GI perforations at 8 mg/kg dose that was elevated over the control population, but similar to the background rate seen in RA databases; and hematologic and biochemical effects, such as on transaminases, neutrophils, platelets, and lipid changes, that are identifiable and manageable in clinical practice by dose modification and/or interruption of tocilizumab or concomitant medications; or, for the case of the lipid abnormalities, lipid-lowering agents as appropriate, and treating these patients to current local guidelines.

We also have in place, or are putting in place, as you heard from Dr. Van der Auwera, a robust pharmacovigilance and risk mitigation plan.

So in summary, this data supports a positive benefit risk assessment supporting the use of tocilizumab at 8 mg/kg every four weeks in monotherapy or in combination with other DMARDs to reduce the signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs or anti-TNF agents, or in whom DMARDs are not considered appropriate. In some DMARD IR patients, a dose of 4 mg/kg may be considered, followed by adjustment to 8 mg/kg based upon clinical response.

I'd like to thank the Committee for their attention this morning, and the Roche team stands ready to answer any questions that you may potentially have on either the molecule or the development program.

Thank you.

DR. WILLIAMS: Thank you. The Committee may now address any questions they have to the sponsor. Dr. Hoffman?

DR. HOFFMAN: I didn't see, either in the materials that were provided to us or in the presentation, what the list of exclusions were. Obviously, that has important implications in terms of the safety profile. Do we know? Can you tell us whether or not patients were included or excluded for congestive heart failure, angina, recent MIs, peripheral vascular disease, chronic obstructive lung disease, uncontrolled diabetes, et cetera?

DR. WILLIAMS: Could you identify yourself?

DR. KRASNOW: Yes, my name is Joel Krasnow from Roche. The inclusion criteria and exclusion criteria -- I will address the ones you specifically have addressed. In essence, anyone with any of those disease factors -- congestive heart failure, angina, COPD, et cetera -- were permitted in the trial as long as they were able to actively participate and had a life expectancy that would allow them to complete the trial -- a life

expectancy of a year or longer. In addition, we also had specific inclusion and exclusion criteria -- slide up -- with respect to infection, as shown here, where we took patients with known or active current or history of recurrent bacterial, viral, or fungal, mycobacterial, or other infections and excluded these patients.

We also excluded patients with hepatitis B and C and herpes zoster, and also patients with any major episode of infection requiring hospitalization with IV antibiotics within two weeks prior to screening. And the laboratory data that was used for exclusionary purposes is also listed, as well as the serology.

DR. HOFFMAN: Thank you. So a follow-up to that question is, when you look at the impact of particular common co-morbidities on adverse events, can you tell us whether or not you have enough patients in your studies with those co-morbidities so that there is or is

not skewing of adverse events in those patients who have, for example, congestive heart failure, chronic obstructive lung disease, particularly in regard to cardiovascular endpoints as well as infectious diseases, particularly pneumonias and bronchitis?

DR. WILLIAMS: Dr. Krasnow?

DR. KRASNOW: Yes, thank you. When we looked at the baseline disease characteristics for patients entering the study, we found that the disease characteristics were balanced across treatment groups with respect to, as you have mentioned, cardiovascular illness as well as previous infections.

DR. WILLIAMS: Dr. Weisman?

DR. WEISMAN: The GI perforations signal that you mentioned brings to mind the possibility that maybe there are receptors for IL-6 or gp130 receptors in the GI tract, and the GI tract may be vulnerable in this situation. And I think -- I just want to ask if the company has looked into this. Is there a relationship,

and if so, how can we understand it going forward?

DR. WILLIAMS: Dr. Leff?

DR. LEFF: Jonathan Leff, Roche. We did study this in the pre-clinical program, in two species. And in the pre-clinical program, with high exposures to TCZ, there is no effect on the integrity or the motility of the GI tract. As well, there was a mouse knockout model generated, and again the GI tract appeared normal in that setting.

So it didn't appear that there was any functional purpose or mechanism of action of IL-6 relative to the GI tract.

DR. WILLIAMS: Dr. Felson?

DR. FELSON: I have a couple of questions for you, one about efficacy and one about side effects. Since we're not going to spend any time later talking about efficacy -- and I think you did a nice job presenting what appears to be pretty clear-cut efficacy -- I wanted to just ask you a couple of

questions about that. If you could go back to your slide P39 -- so one of the continued summary points that you make is that the 4 mg/kg dose is less efficacious than the 8 mg/kg dose, which is what you recommend.

And I guess I was not persuaded by these data, and I wanted to just have you help me know why you continued development with a higher dose that may or may not be a more toxic dose, especially given all the toxicity concerns that have arisen.

So the main reason -- so the ACR 20/50/70 and the DAS measures that you used as your primary measures of efficacy in these trials are all composite measures which incorporate the CRP, and the CRP has a dynamite response to this therapy because it's IL-6-dependent. So if you look at the far right, you see that dynamite response at 8 mg/kg versus 4 mg/kg, a very, very dramatic difference.

If you look at all of the symptom