FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC)

Wednesday, August 2, 2017

8:00 a.m. to 3:32 p.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. SOLOMON: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd like to identify the FDA press contact, Theresa Eisenman.

Are you in the room? Okay. There she is. If you are present, please stand. You have. Okay.

My name is Dan Solomon. I'm the chairperson of the Arthritis Advisory Committee, and I'll now call the August 2, 2017 meeting of the Arthritis Advisory Committee to order. We'll start by going around the table and introducing ourselves, and we'll start with the FDA to my left at the end of the table and go around the room.

DR. ROSEBRAUGH: Good morning. Curt Rosebraugh, director of Office of Drug Evaluation II.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm

the director, Division of Pulmonary, Allergy, and Rheumatology Products.

DR. MAYNARD: Good morning. I'm Janet Maynard, clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products.

DR. BORIGINI: I'm Mark Borigini, clinical reviewer in the Division of Pulmonary, Allergy, and Rheumatology Products.

DR. LEVIN: Greg Levin, associate director, Division of Biometrics II, FDA.

DR. MEISEL: Steve Meisel, patient safety, director of Fairview Health Services in Minneapolis.

DR. OLIVER: Alyce Oliver, Medical College of Georgia at Augusta University, Division of Rheumatology.

DR. JONAS: I'm Beth Jonas from the University of North Carolina at Chapel Hill, Division of Rheumatology, Allergy, and Immunology.

DR. WALDMAN: Scott Waldman, clinical pharmacology, Thomas Jefferson University, Philadelphia.

DR. SOLOMON: Dan Solomon, rheumatologist, clinical scientist at Brigham and Women's Hospital.

DR. BAUTISTA: Phil Bautista, acting designated federal officer for this committee.

DR. BECKER: Mara Becker. I'm at Children's Mercy Hospital in Kansas City, Missouri in the Divisions of Pediatric Rheumatology and Clinical Pharmacology.

DR. KATZ: James Katz. I'm a staff clinician at NIH and program director for the rheumatology training program.

DR. HORONJEFF: Jen Horonjeff, a patient center outcomes researcher at Columbia University Medical Center in their Department of Medicine, and also the consumer representative with multiple rheumatic diseases.

MS. ARONSON: Diane Aronson, patient representative from Naples, Florida.

DR. WEISMAN: Michael Weisman, rheumatologist, Cedars-Sinai Medical Center, Los Angeles.

DR. SUAREZ-ALMAZOR: Good morning. I'm

Maria Suarez-Almazor, rheumatologist, University of Texas, MD Anderson Cancer Center.

DR. BRITTAIN: I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

DR. FELSON: I'm David Felson. I'm a rheumatologist and clinical epidemiologist at Boston University.

DR. CURTIS: Good morning. Sean Curtis. I'll be serving as the industry rep. I work at Merck Research Labs in scientific affairs.

DR. SOLOMON: Great. Thanks for those intros. It's great to have everyone here.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and 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, and 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 of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, 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.

I'll now pass it to Phil Bautista, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. BAUTISTA: Thank you.

The FDA is convening today's meeting of the Arthritis 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 this

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 the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that the members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC 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 special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the

integrity of the services which the government may expect from the employee.

Related to the discussions 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 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, speaking, teaching, writing, patents and royalties, and primary employment.

Today's agenda involves BLA 761057 for sirukumab injection, proposed trade name Plivensia, submitted by Janssen Biotech, Incorporated, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs. The discussion will include dose selection, efficacy, radiographic progression study, and safety.

This is a particular matters meeting during which specific matters related to Janssen's BLA 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. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the invited industry representative, we would like to disclose that Dr. Sean Curtis is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Curtis' role at this meeting is to represent industry in general and not any particular company. Dr. Curtis is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussion involves 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 other financial relationships that they may have with the firm at issue. Thank you.

DR. SOLOMON: Thank you.

We'll now proceed with the FDA's opening remarks from Dr. Janet Maynard.

FDA Introductory Remarks - Janet Maynard

DR. MAYNARD: Good morning. My name is Janet Maynard. I'm a clinical team leader and rheumatologist in the Division of Pulmonary, Allergy, and Rheumatology Products. I would like to welcome you to the Arthritis Advisory Committee meeting for BLA 761057 for sirukumab. I will provide FDA's introductory remarks for this Arthritis Advisory Committee meeting.

As background, rheumatoid arthritis is a chronic, systemic, inflammatory disease that

primarily affects the synovial joints. Rheumatoid Arthritis can result in permanent joint damage and disability. Multiple therapeutic options have been approved for rheumatoid arthritis over the last 20 years.

Today we will discuss sirukumab. The proposed trade name is Plivensia. Sirukumab is a human monoclonal antibody against IL-6. In contrast, the two approved IL-6 inhibitors target IL-6 receptors. The proposed indication is the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying antirheumatic drugs. The proposed dosage is 50 milligrams subcutaneously every 4 weeks.

This slide provides an overview of the sirukumab clinical program. The program includes a phase 2 study, two placebo-controlled phase 3 studies, an active-controlled phase 3 study, a long-term safety study, and an additional safety study in Japan. I will provide an overview of

these studies on the following slides.

This slide provides an overview of the phase 2 study. The phase 2 study included two parts. Part A was a proof-of-concept study comparing sirukumab 100 milligrams every 2 weeks to placebo. Part B was a dose-ranging study evaluating sirukumab 25 milligrams, 50 milligrams, and 100 milligrams every 4 weeks, 100 milligrams every 2 weeks, and placebo.

The two placebo-controlled phase 3 studies evaluated sirukumab 50 milligrams every 4 weeks and sirukumab 100 milligrams every 2 weeks versus placebo. Study 3002 was placebo controlled for 52 weeks, and study 3003 was placebo controlled for 24 weeks. Patients on placebo had an escalation in treatment based on escape criteria at multiple time points in both studies. You will hear additional discussion of the design of these studies in the FDA presentations later this morning.

Study 3005 compared sirukumab 50 milligrams every 4 weeks and 100 milligrams every 2 weeks to adalimumab. In this study, patients did not

receive background methotrexate. Study 3001 was a safety study in Japan, and study 3005 was a long-term extension study for patients initially randomized to 3002 and 3003.

I will now highlight some key efficacy and safety considerations to provide a framework for the committee's discussion today. We will start with efficacy considerations. Study 3002 and 3003 provided evidence of sirukumab's efficacy for signs and symptoms, physical function, and radiographic outcomes in rheumatoid arthritis. The two studied doses, sirukumab 50 milligrams every 4 weeks and 100 milligrams every 2 weeks, showed similar efficacy. Janssen has only proposed approval of the 50 milligrams every 4 weeks dose.

In an active comparator study, the effects of sirukumab and adalimumab on signs and symptoms were similar. In this study, sirukumab was not superior to adalimumab for signs and symptoms of rheumatoid arthritis.

Moving to safety considerations, in the sirukumab clinical program there was an imbalance

in all-cause death with sirukumab over placebo. The rate of all-cause death was similar with both doses of sirukumab. The major causes of death included cardiovascular events, malignancy, and infections. Also, sirukumab was associated with imbalances in serious adverse events and gastrointestinal perforation.

In addition, sirukumab was associated with laboratory abnormalities, including decreases in neutrophil and platelet counts and increases in lipid parameters -and liver function tests.

In the framework of these efficacy and safety considerations, there are several issues we hope the committee will discuss this afternoon. These include the efficacy of sirukumab for adults with rheumatoid arthritis and the design of the 52-week placebo-controlled radiographic study. In addition, we ask the committee to consider the safety findings in the sirukumab program with particular consideration of the imbalance in all-cause death between sirukumab and placebo.

Another discussion point for this meeting is

the dose selection for phase 3. Lastly, we will consider the overall risk-benefit of sirukumab for adults with moderately to severely active rheumatoid arthritis.

As per the Code of Federal Regulations, this advisory committee meeting is being utilized to conduct a public hearing on matters of importance that come before FDA to review the issues involved and to provide advice and recommendations to the commissioner. The commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.

Thank you for your attention. I will now turn the meeting back to Dr. Solomon.

DR. SOLOMON: Thank you, Janet.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA

encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Janssen's presentation.

Applicant Presentation - George Vratsanos

DR. VRATSANOS: Good morning. I'm George Vratsanos from Janssen clinical development and a rheumatologist by training. On behalf of Janssen and our co-development partners, GlaxoSmithKline, we thank the committee and the FDA for this

opportunity. We look forward to presenting the results from our development program for sirukumab, a monoclonal antibody that targets IL-6 for the treatment of rheumatoid arthritis. In this introduction, I will provide a brief overview of the rationale for the development of sirukumab in RA, describe the attributes of the molecule, and then summarize its development history.

The availability of biologics has transformed the lives of RA patients. They reduce signs and symptoms, they inhibit the progression of structural damage, and they improve quality of life. We are proud that Janssen has been part of this transformation through the development of several biologics for rheumatoid arthritis beginning with Remicade, but it is simply not enough. More needs to be done.

Patients who require biologics typically cycle through many different treatments over the years, and they often ultimately run out of treatment options to control their disease. This disease typically strikes first in middle age, and

patients must live with it the rest of their lives. There is increasing awareness that from a patient's perspective, current treatment options do not fully address their needs.

The role of the IL-6 pathway in the pathogenesis of RA is well established. Depicted here is a simplified cartoon showing both the local effects on the joints as well as some of the key systemic effects. In the joints, as shown on the left, IL-6 contributes to cartilage degradation, synovial inflammation, and bone destruction. In addition to these local effects, elevated circulating levels of IL-6 have been linked to several detrimental systemic effects.

Fatigue and potentially depression have been linked to IL-6, and IL-6 is definitely causally related to the anemia of chronic disease. There are two forms of the IL-6 receptor, a transmembrane form shown on the left and a soluble form as shown on the right. Both can bind IL-6 and signal through the JAK-STAT pathway.

To date, the only approved products that

target the IL-6 pathway for RA are monoclonal antibodies directed against the IL-6 receptor. These antibodies shown in orange bind to both the membrane and the soluble forms of the receptor, and they prevent its interaction with IL-6.

Other ligands can bind the receptor. The biology of these interactions is unknown. With this knowledge and leveraging Janssen's experience in developing monoclonal antibodies against cytokines, we discovered and developed sirukumab, the first biologic to target the IL-6 cytokine.

Sirukumab, shown here in light blue, targets the IL-6 pathway by directly binding the IL-6 cytokine. Like the IL-6 receptor antibodies, it prevents the binding of IL-6 to both the membrane bound and the soluble forms. Sirukumab does not bind the other ligands of the IL-6 receptor.

Sirukumab is a human IgG1 kappa monoclonal antibody. It binds to all isoforms of IL-6 with high affinity and specificity, and it demonstrates linear pharmacokinetics when given IV or subQ over the dose ranges studied. Bioavailability is good,

approximately 90 percent when given subQ, and steady state is reached by 12 weeks. The half-life is approximately 15 to 19 days when given subQ. Collectively, these pharmacokinetics support every 4-week dosing.

The overall incidence of antibodies directed against sirukumab is low, approximately 2 to 3 percent, when given in combination with or without methotrexate.

We developed sirukumab with two well-established presentations to meet the needs of RA patients, a pre-filled syringe and an autoinjector. The autoinjector was specifically designed for use by RA patients. Both of these devices are currently in use in the market, including Simponi.

I'll now provide a brief overview of the clinical development program. We engaged with the FDA on multiple occasions to seek their input regarding the design of our program. Additionally, we engaged with health authorities in the EU and Japan and integrated this feedback into our global

registrational program.

The objective of the phase 1 program was to evaluate the safety and pharmacokinetics of sirukumab. The phase 2 trial was designed in two parts. The first was proof of concept, and the second was dose ranging to inform dose selection for phase 3. We designed the phase 3 program to rigorously assess both safety and efficacy. We studied patients with extensive pretreatment histories, including those patients who may have tried multiple biologics.

We purposely included a comprehensive assessment of endpoints that are clinically meaningful to patients to address several aspects of their unmet need. I will return to review the results of the efficacy later this morning.

Regarding safety, a large safety database currently reflects over 5,000 patient-years of experience with additional experience accruing from a long-term extension. Dr. Yeilding will review the integrated safety profile of sirukumab, including the identified and potential risks.

As indicated by the FDA's questions to this panel, this meeting has two objectives. The first is to evaluate the efficacy and safety of the product, and secondarily, to provide guidance to future sponsors regarding dose selection and the design of RA clinical trials.

For efficacy, we will emphasize the extensive number of treatments that patients may have tried before coming into the pivotal trials. This speaks to their unmet need and puts the efficacy in context. For safety, we will focus on the mortality data and present thorough analyses of the main causes of death, including serious infections, MACE, and malignancy.

Today, we will show you the data that demonstrate the positive benefit-risk of sirukumab for the following indication: the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying, antirheumatic drugs.

Dr. Sergio Schwartzman from the Hospital for

Special Surgery will present a clinical rheumatologist perspective on the unmet need. I'll then return to present the key efficacy results. Dr. Newman Yeilding will present the integrated safety, and I'll return at the conclusion to provide some brief closing remarks.

The team at Janssen today is supported by a distinguished panel of external experts who are here today to help address your questions. They are Dr. Gary Koch from the University of North Carolina; Dr. Don Mager from the University of Buffalo; Dr. Paul Ridker from Harvard Medical School; Dr. Brian Strom from Rutgers; Dr. Raj Vuppalanchi from the Indiana University School of Medicine; and Dr. William White from the University of Connecticut.

I now invite Dr. Schwartzman to present on the unmet need in RA.

Applicant Presentation - Sergio Schwartzman

DR. SCHWARTZMAN: Good morning. My name is Sergio Schwartzman. I'm a rheumatologist at the Hospital for Special Surgery, the Weill Cornell

Medical College, and the New York Presbyterian Hospital. I am here on behalf of the sponsor, and I am being compensated for this activity.

My role today is to discuss some of the issues related to the dynamics of rheumatoid arthritis and also the concept of unmet need that still remains for the management of patients who have rheumatoid arthritis.

This slide delineates my disclosures, but further, it also gives you a perspective on the evolution of the management of rheumatoid arthritis. In the three decades that I have been a rheumatologist, I've seen the movement from high-dose aspirin and gold therapies to the era that now exists with biologics and targeted synthetic DMARDs.

Rheumatoid arthritis is perhaps one of the most common autoimmune diseases that rheumatologists deal with. Indeed, it affects 1 percent of the world's population, and in the United States, it is estimated that between 1.3 and 1.7 million people are living with this disease day

to day. It can lead to lifelong disability even in this day and age. The mortality has increased in this group of patients, and this is in part due to infections, cardiovascular events, and malignancies that frequently are due to the disease itself. RA is a disease that on the one hand targets the joints, but more importantly, this is a systemic illness that has not only physiologic consequences but social repercussions as well.

Again, by way of background, then, our current therapeutic approach to this disease has evolved. Our targets remain the same. We want to lower inflammation, relieve pain, prevent joint damage, and improve quality of life. We want to further address the comorbidities associated with this disease.

Different strategies have been promulgated. The treat-to-target approach has gleaned a lot of interest. And from a philosophical perspective, it does make sense to pick a target and then change therapy accordingly, depending on whether or not that target is met. Unfortunately, the reality, at

least in the United States, is that this approach is not frequently used in the management of patients in the clinics of patients that are being treated for rheumatoid arthritis. So treatment goals are not being met, and indeed the majority of RA patients, even in some of the European studies that are looked at, do not achieve remission.

What then are the unmet needs? From the physician's perspective, there are many patients that cycle through multiple therapies. And although the initial treatment is methotrexate, five years out, approximately 50 percent of patients who are started on this drug are no longer taking it.

The second-line agents, including the biologics and the targeted synthetic DMARDs, have also relatively high discontinuation rates, and patients may try new therapies every two to three years within this group of therapeutic agents. Once these patients fail one agent, they are less likely to respond to a second. Eventually, patients do run out of therapeutic options.

From the perspective of the patient, there are somewhat different unmet needs that are being increasingly recognized. This slide summarizes a paper by Taylor that actually looked at some of the patient concerns, which tend to be, on the one hand, more subjective in nature but have much greater impact on the patient's day-to-day life. These include issues such as pain, physical function, mental function, fatigue, and social function. Minimally clinically important differences in these components are infrequently met in clinical trials.

With regards to highlighting this, there has been a move in rheumatology to include them more and more in clinical trials. I do have fatigue, for example, utilizing the FACIT scale that has been incorporated into many of the clinical trials that we now see in patients with rheumatoid arthritis. Mental function, for example, depression, is very frequently unrecognized in the RA community of patients. There may be a role for different cytokines in these comorbidities,

including interlukin-6.

So what is my summary, what is my perspective, on sirukumab? Having reviewed the data that you will now see, the efficacy is comparable to other biologics. It does have the robust benefit in ACR scores, radiographic scores and structural damage, and measurements of quality of life. It has benefits in both DMARD IR and TNF IR patients. It works both as combination therapy and as monotherapy. And from a safety perspective, it does represent the types of safety events that rheumatologists over the last two decades, when we have been using biologics, have now become comfortable identifying and helping to manage.

Rheumatoid arthritis remains a challenging and frustrating disease that continues to require new therapeutic options, and I would say that sirukumab may help meet that unmet need in RA. Thank you.

I will now invite George Vratsanos to come back up and present the efficacy data on sirukumab.

Applicant Presentation - George Vratsanos

DR. VRATSANOS: As Dr. Schwartzman noted, despite the availability of many different therapies for RA, many patients eventually run out of treatment options and suffer serious consequences. There remains a compelling unmet need for new treatments with new mechanisms of action. Therefore, in our clinical development program, we intentionally studied patients with extensive pretreatment histories to reflect the current place and practice for a new RA therapeutic.

I'll begin by describing the key questions and outcomes that drove the design of our phase 3 program. I'll then review our rationale for selecting the 50-milligram q4 and 100-milligram q2 doses for phase 3. This topic has been noted in the FDA's briefing book as important for discussion by this committee.

In the third section, I'll focus on the key results from the two placebo-controlled pivotal trials. These form the foundation supporting the

effectiveness of the product. They were conducted in patients with an inadequate response to disease-modifying antirheumatic drugs or DMARDs; that's study 3002. And also in study 3003, we studied patients with an inadequate response to anti-TNF therapies.

Time does not permit review of the active comparator study, study 3005. This was conducted in monotherapy. The results from this study are summarized in our briefing book as well as in the FDA's. I'll conclude with a summary of the efficacy supporting our proposed dose recommendations of 50 milligrams q4.

We designed the two placebo-controlled trials to address the following two questions. First, is sirukumab safe and effective in patients with an inadequate response to non-biological DMARDs? Study 3002. And second, is sirukumab safe and effective in patients in whom anti-TNF therapy is not an option due to inadequate response? That is study 3003.

The first major outcome we wish to assess

was effectiveness in reducing signs and symptoms. This means reducing the number of tender and swollen joints, reducing pain, improving physical function, improving the patient's and the physician's global assessment of disease activity, and reducing systemic inflammation. The standard measures are the ACR20, 50, and 70, corresponding to 20, 50, and 70 percent improvement overall, respectively, in signs and symptoms.

The second major objective was to test the efficacy in inhibiting the progression of structural damage. This was measured using an accepted instrument by health authorities, the van der Heijde modified total Sharp score.

The third major outcome was to assess the efficacy in improving patient-reported outcomes. We used the following validated instruments. The SF-36 was used to assess the impact on both the physical and mental components of health-related quality of life, the FACIT-F questionnaire was used to assess fatigue, and physical function was assessed using the Health Assessment Questionnaire.

I'll now show you a summary of our results before proceeding with a trial-by-trial overview. In two different difficult-to-treat patient populations, sirukumab demonstrated statistically significant and clinically meaningful benefits in reducing signs and symptoms, inhibiting joint damage, and achieving low disease activity. All prespecified primary and major secondary endpoints in the testing hierarchy were achieved as indicated by the black check marks.

Prespecified patient-reported outcomes not in the testing hierarchy are shown in the lower part of the slide. For these outcomes, statistically significant with a nominal p-value of less than 0.05 is shown by the red check mark.

The next series of slides describe the phase 2 design, key results, and implications for the design of our phase 3 program. The phase 2 dose-ranging study evaluated 151 patients with an inadequate response to methotrexate. They remained on background methotrexate during the study. They were randomized equally to 1 of 5 groups shown here

top to bottom: placebo; 100 milligrams q2 weeks in black; 100 q4 in purple; 50 q4 in red; and 25 q4 in orange.

The top dose was selected to provide maximal inhibition of the CRP with appropriate safety margins following phase 1 studies. The primary endpoint is shown at the bottom. It was the ACR50 at week 12. All patients on placebo were switched to sirukumab 100 q2 after week 12, and the trial was double blind to sirukumab dose through week 24.

This figure plots the proportion of patients achieving the ACR50, the primary endpoint, over time. ACR50 response is on the Y-axis and time is shown on the X-axis. The ACR50 represents the proportion of patients achieving at least a 50 percent reduction of signs and symptoms focusing first on the primary endpoint at week 12, all doses separated from placebo, which is shown in blue, and had similar efficacy.

The two dose schedules that were statistically significant were 100 q2 and 50 q4. From week 12 to 24, note that the original placebo

group, now shown by the blue dashed line, achieved a strong response after switching to sirukumab.

To gain a more complete evaluation of efficacy, we followed the ACR50 to week 24. At week 24, a dose response is observed. The highest dose regimen, 100 q2 in black, achieved the highest response, 60 percent. The next highest regimen, 100 q4 in purple, achieved a 10 percent lower response. The two lowest doses, 50 q4 and 25 q4, in red and orange, respectively, achieved comparable lower levels of efficacy, 30 to 36 percent on the ACR50.

We also examined dose response by examining changes in disease activity over time. The Clinical Disease Activity Index, or CDAI, is a continuous measure of disease activity that is more sensitive generally to detect differences between doses. We also analyzed the CDAI because it excludes the CRP, unlike the ACR responses. This was done to separate the pharmacodynamic effects of sirukumab on the CRP from its impact on other clinical measures.

This figure plots the improvement in the CDAI over time with improvement shown as a negative change on the Y-axis. Focusing first on week 12, the doses again have comparable efficacy and all separate from placebo.

Note that there is a numerical advantage for the highest dose regimen of 100 q2 in black. Importantly, at week 24, we saw a trend for dose response from 100 q2 in black to 25 q4 in orange. So in this analysis, as well as in the ACR50, we observed that 25 q4 had the lowest efficacy. We also analyzed disease activity when the CRP was included.

Shown here is the change in DAS28 CRP over time. We observed the same pattern. The dose schedules perform comparably at week 12. The placebo group improved after crossing over to sirukumab, and at week 24, we observed a dose response. The 25 q4 group in orange did not meaningfully improve from week 12 to 24. The reduction in disease activity with 25 q4 was less than 50 q4, and the efficacy with 50 q4 did not

appear as good as the efficacy with 100 q2 or 100 q4.

We next analyzed exposure response. A clear picture emerged from exposure response analyses. Lower exposures led to lower response. This was demonstrated by examining the relationship between trough exposure, shown in quartiles on the X-axis, and clinical response. Shown here are two clinically relevant endpoints, the ACR50 and the proportion of patients achieving low disease activity as measured by a DAS28 CRP of less than 2.6.

The two most important points that are further detailed in figure 7 of our briefing book are that, first, the distribution of exposures with 25 q4 would most often fall within the lowest two exposure quartiles; and second, that 100 q2 would most often fall within the highest quartiles. We also examined biomarker data.

Shown here are the effects of sirukumab on two disease-relevant biomarkers, the CRP and matrix metalloproteinase 3. The literature suggests that

baseline MMP-3 is an independent predictor of the progression of structural damage, therefore, measuring changes in MMP-3 may have prognostic value.

This figure shows a percent change in the biomarker from baseline to week 12. On the left, you can see that all 4 doses performed equally well in suppressing the CRP by more than 95 percent. On the right, for MMP-3, a different pattern was observed. The 25 q4 dose in orange behaved like placebo in blue. In contrast, greater than 50 percent suppression off MMP-3 was observed in the higher dose groups. This suggested that a dose schedule of 50 q4 or higher would have greater impact on structural damage.

Safety was an important consideration in our dose selection. We recognize the limitations of a phase 2 study to properly evaluate safety. With 34 weeks of exposure, we did not observe any major trends for differences between the doses in the frequency of adverse events, serious adverse events, discontinuation, and serious infection.

I'd like to pause for a moment and summarize the conclusions from the phase 2 study. First and foremost, the efficacy was strongly suggestive of pursuing sirukumab in phase 3 for further clinical development. The top dose of 100 milligrams every 2 weeks achieved the highest efficacy with a compelling ACR50 response of 60 percent. Safety was similar across all four regimens, and therefore the 100 q2 schedule was a logical choice for the top dose to study in phase 3.

The 50 q4 had good activity, was statistically significant on the primary endpoint, and had substantially less exposure than 100 q2. We wanted to study a dose range in phase 3 that would be non-overlapping in terms of exposure, and with biologics, this typically requires a 3 to 4-fold reduction in total dose to achieve meaningfully lower exposures. Therefore, the 50 q4 dose was chosen.

The 25 q4 dose was not chosen because of the totality of the data. The clinical data demonstrated it had the least impact on disease

activity. This was supported by exposure response analyses, which demonstrated that patients with the lowest trough exposure would have the lowest efficacy on clinically meaningful endpoints.

This was further supported by analysis of the biomarker data. The 25 q4 dose had the least impact on a biomarker associated with joint damage. This suggested it may not be effective in inhibiting the progression of structural damage. Therefore, given the totality of the data and with a caveat of relatively small numbers of patients in a phase 2 study, we chose 50 q4 and 100 q2 for investigation in phase 3.

I'll now turn to the design of the phase 3 program. Here is the architecture of the phase 3 program. Our goal was to evaluate the efficacy of sirukumab in two independent placebo-controlled trials. The DMARD IR study was study 3002 and the TNF IR study was study 3003.

Our main focus today is on these two trials, the two placebo-controlled trials. We also studied monotherapy patients by conducting prespecified

placebo-controlled subgroup analyses from studies 3002 and 3003. These are the main data supporting efficacy and monotherapy. We also conducted an active comparator study, study 3005, versus adalimumab, which is supportive of efficacy in monotherapy. In the active comparator study, sirukumab had comparable efficacy to adalimumab but was not superior. Details of these studies are in our briefing book.

I'll now describe study 3002. To determine whether or not sirukumab was effective in inhibiting joint damage, we conducted a placebo-controlled trial in patients with an inadequate respond to DMARDs. We randomized 1670 patients equally to 1 of 3 arms, placebo 100 q2 or 50 q4 of sirukumab. Patients were allowed to stay on background DMARDs. There was no group receiving placebo alone.

In addition, we did not exclude patients who may have tried other biologics. Patients may have tried one biologic and discontinued for safety or tolerability but not for lack of efficacy. The

patient population shown in the text box on the left was specifically chosen to be at higher risk for radiographic progression. All patients were required to have an elevated CRP and must have had either rheumatoid factor, anti-CCP antibodies, or erosions at baseline.

Placebo patients were required to escape to sirukumab at week 18 if they were not improving or at week 40. In addition, all patients could adjust their background therapies at week 28. The ACR20 response at week 16 was the first co-primary endpoint, and the second was the mean change in van der Heijde Sharp score from baseline to week 52.

Baseline disease characteristics were well balanced across the three treatment groups. These patients had systemic inflammation with a mean CRP of 2.5 milligrams per deciliter and had high disease activity with a mean DAS28 CRP of 5.8 to 5.9. As shown at the bottom, approximately two-thirds of patients had tried two or more DMARDs before coming into the trial. Thirty-one to 38 percent had prior exposure to biologics, and

these data demonstrate the extensive pretreatment histories of these patients.

Thirty-four percent of patients on placebo required escape at week 18 because they were not improving. Fifteen percent of patients on 50 milligrams and 10 percent of patients on 100 milligrams q2 also met escape criteria. After this early escape point, discontinuations were comparable between the three groups.

Note at the bottom of the slide that only about one-half, 49 percent, of patients on placebo were able to stay on placebo for the entire year. Eighty-four to 86 percent of patients on sirukumab completed one year of their randomized treatment.

The major efficacy outcomes are shown in the next series of slides. The primary endpoint of the study, the ACR20 at week 16, is shown at text box at the left. ACR responses at week 24 are shown on the right. Both the 50 and the 100-milligram dose schedules were significantly more effective than placebo on the ACR20 with an absolute difference in response of 28 to 29 percent versus placebo.

Looking at week 24 on the right, both doses performed equally well on the ACR50 and remain statistically significant with an actual p-value of less than 0.001 that was multiplicity controlled. This analysis was prespecified.

In addition, efficacy was demonstrated in all other supportive analyses of secondary endpoints at week 24 such as the ACR20 and the ACR70. These nominal p-values were all less than 0.001. Multiple sensitivity analyses confirmed the robustness of this result, and details are in our briefing book.

I'll turn to the co-primary endpoint, the efficacy at one year in inhibiting joint damage. One of the critically important goals in RA is to inhibit the progression of joint damage. If left unchecked, progressive joint damage usually leads to irreversible loss of function and potentially disability.

We studied if sirukumab could inhibit joint damage by measuring the mean change in the van der Heijde Sharp score from baseline to one year.

Worsening joint damage is shown as a positive change on the Y-axis. Data were imputed with linear extrapolation for placebo patients who crossed over to sirukumab.

As shown on the left, both the 50- and the 100-milligram dose schedules were equally effective, and both were significantly more effective than placebo in inhibiting radiographic progression. Efficacy was also significant at 6 months as describe in our briefing book.

We conducted an extensive set of sensitivity analyses to examine the robustness of this result. As an example, shown on the right, if instead of linear extrapolation we use the observed value at one year for placebo patients who crossed over to sirukumab, even then the results remain statistically significant.

Improved quality of life is an important aspect of unmet need in RA. An improvement of at least 5 units in the physical component score, PCS, of the SF-36 and 5 units in the mental component score, MCS, is considered clinically meaningful.

These were prespecified analyses.

Shown on the left, patients on sirukumab were more likely to have clinically meaningful improvement in both the physical and the mental components of health-related quality of life. Both doses were equally effective. In addition, shown on the right, improvements versus placebo were also noted in all 8 domains of the SF-36. Nominal p-values were all less than 0.05. This demonstrates the consistency of this benefit on all aspects of health-related quality of life.

With respect to fatigue, more than 50 percent of RA patients report fatigue as their most problematic symptom. The FACIT-F questionnaire has been validated in RA, and an increase of 4 units of more is considered clinically meaningful.

As shown in this figure, plus the percentage of patients achieving clinically meaningful improvement in the FACIT, more patients on sirukumab were able to achieve this important clinical threshold. Again, both doses were equally

effective.

I'll now turn to the design and key results from study 3003 in patients with an inadequate response to anti-TNF therapies. This trial studied an even more heavily pretreated population than study 3002. Key inclusion criteria are shown in the text box at the left. All patients in the trial had not responded well to at least one TNF inhibitor or could not tolerate two or more anti-TNF therapies.

Importantly, patients may be eligible if they had tried other biologics in addition to an anti-TNF. We randomized 1878 patients equally to 3 arms: placebo, 100 q2, and 50 q4. The study was placebo controlled through week 24 and blinded to sirukumab dose through week 52. The primary endpoint, as shown at the bottom, was the ACR20 at week 16.

Similar to the DMARD IR trial, patients were required to escape at week 18 if they were not improving. At week 24, as shown at the top, all remaining patients on placebo were randomized to

one of the two sirukumab arms. After week 24, adjustments could be made in background RA therapy.

The baseline characteristics describe a patient population with persistent high disease activity despite extensive pretreatments. The mean duration of RA was approximately 12 years, and the disease activity on average was high, again, with a mean DAS28 CRP of 5.8 to 5.9.

As shown at the bottom, 95 to 97 percent of patients, in addition to biologics, had tried two or more non-biological DMARDs. Almost all patients, 95 percent, had discontinued at least one anti-TNF due to lack of efficacy, and about 40 percent of the population as a whole had tried two or more anti-TNFs. More than one-third, 35 to 41 percent as shown at the bottom, had tried other biologics.

About 290 patients were randomized into each arm. Thirty-two percent of placebo patients required escape at week 18. All remaining patients on placebo crossed over to sirukumab at week 24. At one year, discontinuations were comparable

between the originally randomized groups.

The ACR20 at week 16, the primary endpoint is shown in the text box on the left along with the ACR scores at week 24. At week 16, both doses were significantly more effective than placebo on the ACR20. There was a small numerical advantage to the higher dose at this early time point. At week 24, both doses performed equally well on the ACR20, 50, and 70, and both doses were significant for all comparisons versus placebo on the ACR endpoints.

We observed that 40 percent of patients had indeed tried other biologics, mostly abatacept, rituximab, and tocilizumab. Therefore, we asked how does the efficacy compare if a patient had tried only anti-TNFs versus those patients who had also tried a biologic with a different mechanism of action. Focusing first on the anti-TNF only group on the left, both doses were more effective than placebo. Importantly, on the right, even in patients with other biological experience, sirukumab was effective.

We were also interested to understand if response depended on the number of biologics a patient had tried. Shown here are the odds ratio for the primary endpoint, the ACR20, for the full population shown at the top, the subgroup with one or two or more prior anti-TNFs in the middle and one or two or more total biologics as shown at the bottom. Importantly, efficacy was consistent regardless of the number of biologics a patient had tried.

Consistent with the DMARD IR trial, a significantly greater proportion of patients achieved clinically meaningful improvement in health-related quality of life. This was true for both the physical component score as well as the mental component score. And again, the data, as shown on the right, indicated that significant improvements versus placebo were achieved in all 8 domains of the SF-36. This was a prespecified analysis.

I'll now summarize the efficacy across the two studies. The sirukumab phase 3 program was

designed to not merely test whether a novel mechanism of action therapy was active in rheumatoid arthritis, but to address the higher and more clinically relevant question of whether the drug would be effective in patients with extensive pretreatment histories.

The effectiveness of sirukumab was consistently demonstrated in more than 3,000 RA patients with very different treatment histories reflective of common problems in clinical practice. We've presented today results that demonstrate the effectiveness across all primary and major secondary endpoints across the two studies as shown at the top. And with respect to the 2-dose schedules, the differences in efficacy were small and not consistently observed to warrant the higher exposure with 100 q2.

I now return to the question of what RA patients need from a new therapy. What's most important to them? They want to feel better, both physically and emotionally; be pain free; feel less tired; and get back to as normal a life as

possible. It was therefore gratifying to see that sirukumab demonstrated clinically meaningful benefits on improving fatigue and also improving all dimensions of health-related quality of life.

Thank you for your attention. I now turn to Dr. Newman Yeilding to present the integrated safety of sirukumab.

Applicant Presentation - Newman Yeilding

DR. YEILDING: Good morning. My name is Newman Yeilding, and I'm the global development leader for Janssen immunology. I'll present an overview of the safety for sirukumab and describe why these data give us confidence in the safety of sirukumab when used to treat patients with moderate to severe rheumatoid arthritis or RA.

I'll review the following: our approach to analyzing the safety data; safety during the controlled periods of the clinical trials; safety assessment over time with increasing exposure to sirukumab; and I'll provide a brief safety update from data accrued after submission of our biologics licensing application or BLA. And finally, I'll

place our data in the context of other immunosuppressive agents used to treat patients with moderate to severe RA.

Our studies were designed with three major safety goals. First, to protect the safety of study participants, we used patient selection criteria based on information already known about the safety of blocking the IL-6 pathway from the two approved IL-6 receptor antagonists, and we provided monitoring guidelines for investigators with the intent that these patient selection and risk mitigation plans would be incorporated in the product labeling.

Second, to ensure proper characterization of sirukumab safety, eligibility criteria ensured selection of patients with substantial disease activity so that the potential side effects could be characterized.

Third, we focused on specific events associated with anti-IL-6 induced immune suppression and safety events in RA patients with high disease activity. These included risk

associated with immunosuppression such as infections and malignancies; risks associated with targeting the IL-6 pathway, including certain laboratory abnormalities as well as GI perforations; and risks in patients with RA, including cardiovascular safety and certain malignancies, most particularly lymphoma.

We enrolled patients with moderate to severe RA who have the relevant comorbidities and medical risks and who are receiving typically concomitant medications, as Dr. Vratsanos indicated. Cardiovascular risk factors were common comorbidities, most notably hypertension, which in addition to the inflammatory burden of RA lead to greater risk of cardiovascular disease, and cardiovascular death is the most common cause of death in patients with RA.

In addition, the immunosuppressive drugs used in treating RA such as methotrexate and corticosteroids place patients at greater risk for these infections, and the later also increase risk of peptic ulcer disease in GI perforations.

To properly interpret the safety data sets, we randomized patients to ensure well-balanced risk factors, including inflammatory burden, cardiovascular history, and we included evaluation of dose, schedule, and duration of exposure to sirukumab compared to that of placebo.

The number of patients exposed, the dose, and the duration of exposure to sirukumab in phase 3 was similar to that of contemporaneous RA development programs. As shown in the right-hand column, a total of 2,926 patients were exposed to at least one dose of sirukumab; 2,735 were treated for at least 6 months; over 2,000 for at least a year; and almost 800 for at least 2 years.

In summary, the sirukumab development program is similar in size, duration, and patient characteristics compared with contemporaneous RA development programs for assessing safety events in patients with moderate to severe RA.

Our review today will focus on controlled safety data using the 18-week data pooled from the two large placebo-controlled trials, ARA 3002 and

3003. Use of the 18-week data minimized the biases introduced by moving patients who met escape criteria from placebo on to sirukumab. Controlled safety data from ARA 3005 were analyzed separately because the comparators were different, and these data will be displayed separately in this presentation.

Note that the data provided on pages 92 and 93 of your briefing document included data through the SCS cutoff, the summary of clinical safety cutoff, and reflects approximately 45 weeks of follow-up in this trial. But the data that I'll present today reflect the completed trial with approximately 60 weeks of follow-up.

The second approach evaluated safety with increasing duration of exposure and focused only on the ARA 3002 and 3003 trials, and these data showed data in three trial periods: the placebo-controlled data described above; week 52 data that reflects sirukumab's safety with one year of exposure; and the summary of clinical safety or SCS cutoff, which includes all data approved

through the 2nd of February 2016 and exposures up to approximately 3.5 years, and include observational data in the patients doing well enough to enter the long-term extension study 3004. These later two analyses include data after disruption of randomization from escape and crossover of patients from placebo to sirukumab.

Because of these limitations with the internal placebo reference, we will also present an overview of safety of sirukumab compared to that of other drugs used to treat RA, and for these comparisons, we'll use data from all sirukumab phase 3 trials through the SCS cutoff. For controlled safety analyses, I'll review overall adverse events, adverse events of special interest, and laboratory abnormalities.

Shown on the left panel is an overview of safety during the 18-week placebo-controlled period of ARA 3002 and 3003 before escape through crossovers when there was a single death in each treatment group. The details of these events are described on page 95 of your briefing books.

Overall, there were higher rates of adverse events, treatment discontinuations, and serious adverse events in the sirukumab groups, and these will be reviewed in detail later.

Shown in the right panel is an overview of safety during the completed ARA 3005 trial, which also showed 3 fatalities, one in the sirukumab 100-milligram group from a hemorrhagic stroke and 2 in the sirukumab 50-milligram group, one each from respiratory failure in a patient with underlying pulmonary fibrosis and an infection of erysipelas. Overall rates of adverse events, treatment discontinuations, and serious adverse events were numerically higher in the sirukumab groups.

Adverse events that occurred in at least 5 percent of patients in the ARA 3002 and 3003 trial shown here were generally mild, self-limited, and did not result in treatment discontinuation. The most common events that were increased with sirukumab included injection-site reactions, aminotransferase abnormalities, and neutropenia.

The next slide will list the serious adverse

events that occurred in at least 5 patients during the 18-week control period, and overall rates of serious adverse events were about 1.5 to 2 percentage points greater in the sirukumab groups. This difference results primarily from higher rates of serious infections, and the infections most commonly reported were pneumonia and cellulitis. A table summarizing all serious adverse events has been provided on page 94 of your briefing document.

Adverse events of special interest focused on the events listed here. Shown on this slide in the left panel is an overview of adverse events of special interest during the 18-week placebo-controlled period of ARA 3002 and 3003. Consistent with analyses of serious adverse events, rates of serious infections were higher in sirukumab-treated patients.

Major adverse cardiovascular events, or MACE, were adjudicated by the Cleveland Clinic Clinical Events Committee, and for MACE, there was 1 adjudicated MACE in the placebo group, 2 in 50,

and 1 in the 100-milligram sirukumab group. There were 2 malignancies in placebo and one each in the 50- and 100-milligram sirukumab groups. There were no cases of GI perforations on placebo, 1 in 50, and 3 in the 100-milligram group.

Shown in the right panel, the only notable disparity in rates of adverse events of special interest was the higher rate of serious infections in the 50-milligram sirukumab group compared with adalimumab. This disparity in serious infections was not reproduced by the 100-milligram sirukumab group despite the approximately 4-fold higher dosing intensity. Notable disparities in other adverse events of special interest were not apparent.

For laboratory abnormalities, we compared rates with sirukumab versus placebo in the ARA 3002 and 3003 trials. As with IL-6 receptor antagonists, all lipid parameters increased with sirukumab, including total LDL and HDL cholesterol and triglycerides. Shown here, mean LDL levels increased approximately 20 percent in the first 4

to 8 weeks and remained relatively constant thereafter, and mean HDL levels increased approximately 10 to 12 percent. Importantly, the increases in lipid parameters responded appropriately to lipid-lowering agents.

RA patients generally have increased neutrophil and platelet counts, and as with IL-6 receptor antagonists, decreases in neutrophil and platelet counts were observed with sirukumab. Shown here are absolute neutrophil and platelet counts over time in the ARA 3002 trial, which are similar in the other trials and show that decreases in platelets and neutrophils usually occur in the first 2 to 8 weeks of treatment, and most patients maintain values in the normal range. Importantly, changes did not appear to be associated with clinical sequelae and uncommonly required treatment interruption or discontinuations.

The effect of sirukumab on aminotransferases is shown in this slide. During the 18-week placebo-controlled period of ARA 3002 and 3003, more patients on sirukumab had aminotransferase

abnormalities compared with placebo, which is most apparent with ALT elevations at least 3-fold the upper limit of normal. Rates of AST abnormalities are shown at the bottom of the slide, and they were also higher with sirukumab, though the disparities were not as great as with ALT.

Most aminotransferase abnormalities were transient, and less than 1 percent of patients required treatment discontinuation. In the ARA 3005 trial, aminotransferase abnormalities, at least 3-fold the upper limit of normal, and treatment discontinuations were similar between sirukumab and adalimumab.

All cases of LFT abnormalities that might indicate severe liver injury were adjudicated by three independent hepatologists who were blinded to treatment. Two cases were flagged as probable association with treatment, one each in the placebo and the sirukumab groups with details of these events shown here. No cases were found to meet Hy's law criteria due to plausible alternative explanations. Therefore, these results do not

suggest an association of sirukumab with serious liver injury.

To assess longer term safety in ARA 3002 and 3003 and gain insights into the stability of safety signals on treatment, we evaluated sirukumab safety in three trial periods: the 18-week placebo-controlled period, week 52 data reflecting one year on treatment, and the SCS cutoff data.

Placebo-controlled data through week 18 was the most reliable and most readily interpretable because groups were well balanced for safety risk factors. This balance progressively deteriorates after week 18 in a way that biases against sirukumab since the placebo cohort becomes depleted of patients with high disease activity, and the sirukumab cohorts become enriched for these patients.

The critical question is how to fairly account for events that occur after placebo patients escape or cross over, recognizing that no analyses will fully overcome this bias since each will have shortcomings. We therefore conducted

three types of analyses.

First in the left-hand panel, this is an intent-to-treat analysis in which events that occur in patients randomized to placebo are attributed to the placebo group regardless of escape or crossover and compared to patients originally randomized to sirukumab referred to as sirukumab start-arms in the FDA briefing book. This preserves randomization, but has the disadvantage that events that occur in patients escaped or crossed over to sirukumab are counted in the placebo group.

Second, the analysis in the middle panel does not count events in the placebo arm after patients escape or cross over to sirukumab, and these events are also not counted in the sirukumab arms. This keeps the original randomization integrity of the sirukumab start-arms intact but depletes the placebo arm of patients with the highest disease activity. And furthermore, the duration of follow up for patients on placebo is shortened because of the censoring of follow up after escape or crossover.

Third, the analysis on the right panel, like the second analysis, does not count events in the placebo arm after patients escape or cross over to sirukumab. But unlike the second analyses, these events after crossover or escape are counted in the sirukumab groups.

This is referred to as the combined sirukumab arms in the FDA briefing group. While this analysis accounts for all safety events and attributes them to the correct exposure, it disrupts randomization the greatest both by depleting the placebo group of patients with the highest disease activity and enriching the sirukumab groups for those same patients.

I'll mainly focus on the second strategy for week 52 analyses and use the third strategy for SCS cutoff analyses. However, in your briefing document, we've provided week 52 analyses using both the second and third strategies. For mortality, I'll present analyses using each of these three strategies.

Shown on this slide, under placebo in the

red square, are the numbers of patients that escape or cross over and the timing of their escape or crossover. Note that only 273, or 32 percent, of the original 850 patients randomized to placebo remain on placebo, and patients in the sirukumab arms remain under a randomized dose. At the bottom of the slide are the numbers of patients who continue into the long-term extension versus those who discontinued prior to week 52.

By every parameter of disease activity, the patient population who escape from placebo and initiate sirukumab in week 18 were notably different from the patients who continue receiving placebo demonstrating depletion of the placebo group for patients with high disease activity. Escape patient showed on average approximately 30 percent worsening in their tender and swollen joints, while the patients who continued receiving placebo on average improved approximately 50 percent.

With the DAS28 of 5.1, representing the threshold of severe RA, the average DAS28 score in

patients who escaped was 6.1 versus 4.3 in the patients who remained on placebo. And these disparities are important because epidemiologic studies have shown an association between disease activity measured by DAS28, as well as disability is measured by HAQ with risk of mortality.

Moving now to serious adverse events over time and recognizing the limitations of the placebo internal reference and bias against sirukumab in the analyses beyond week 18, we evaluated whether or not serious adverse events accumulated as a function of duration of treatment.

Shown on the X-axis are serious adverse event rates per 100 patient-years plotted in each of the three analysis data sets. The points show the event rates and the brackets show 95 percent confidence intervals. As described before, in the left panel, event rates were higher during the 18-week placebo controlled period in sirukumab, which was attributable to higher rates of serious infections. However, the week 52 analyses in the middle and the SCS cutoff analyses in the right

demonstrate that the event rates also remain generally stable over time.

The next slide depicts mortality as a function of duration of treatment. The left-hand panel shows data previously shown that mortality rates were the same for placebo and sirukumab-treated patients during the 18-week placebo control period with a single death occurring in each treatment group. The middle panel shows mortality rates through week 52, and the right panel shows mortality rates through the SCS cutoff. During these later two periods, there were no additional deaths on the placebo-treated arm.

In the week 52 data set, there were 3 additional deaths in the 50-milligram group and 5 additional deaths in the 100-milligram group. Now recall that in this analysis, placebo patients who escaped or crossed over are not included. During the SCS cutoff period, the mortality rates did not further increase even though this analysis also included all patients receiving sirukumab,

including patients who escaped or crossed over from placebo.

While each fatality is unfortunate, the small number of events at week 52 -- 1, 4, and 6 across treatment groups -- and the disruption of randomization after week 18 make it problematic to evaluate whether a true difference in event rates exist, but the imbalances triggered additional analyses in an attempt to fully understand these data.

For these, we analyzed the underlying causes of death, risk factors, mortality rates over time, the potential impact of disrupting randomization and a comparison of mortality rates against external references, and an additional assessment of non-fatal infections, MACE, and malignancies.

These later assessments were undertaken because the most common causes of death were cardiovascular infection and malignancy, which are also consistent with expectations in this population and consistent with observations from RA development programs. The causes of the other five

cases are shown in the second sub-bullet.

We also determined whether or not each individual had underlying risk factors related to their cause of death, and we found that for each of the individual deaths resulting from cardiovascular causes and serious infections, the patients affected had known risk factors.

As shown in the second bullet, each of the cardiovascular fatalities occurred in patients with established cardiovascular risk factors, and each of the infection fatalities occurred in patients with other known risk factors such as corticosteriod or DMARD use.

We undertook exploratory analyses to evaluate risk factors associated with mortality using multivariate logistic regression and Poisson regression modeling. These models identified the following risk factors: age, baseline corticosteroid use, and a medical history of hypertension, and importantly higher disease activity as measured by HAQ and DAS28 during the trial.

This later observation may help explain the unexpected but fortunate finding of no additional deaths in the placebo group after week 18 since the patients on placebo with higher disease activity escaped to sirukumab depleting the placebo group of patients with high disease activity. Finally, none of these analyses revealed an association between exposure to sirukumab and mortality.

To further determine if there was a demonstrable impact of treatment with sirukumab on mortality, we also tested whether or not mortality rates increased as a function of duration of treatment. Shown here, mortality rates per 100 patient-years of follow-up as a function of time by 6-month increments, mortality rates did not increase over time.

Combined, the types of deaths observed were typical for what one would expect in RA, and the incidence did not appear to increase with duration of use. To attempt to discern how loss of randomization due to escape or crossover placebo patients may have impacted mortality imbalances, we

evaluated week 52 mortality rates in the three ways that I described on slide 75.

As shown in the left panel -- or in other words, the intent-to-treat analysis -- no imbalance is observed. The middle panel shows the imbalance observed between placebo and sirukumab described above, and recall that in this analysis, the placebo group is depleted of escape and crossover patients with the highest disease activity who may have a higher rate of mortality.

As shown in the right panel -- or in other words, counting events in placebo patients who escaped into sirukumab -- the imbalance becomes slightly more pronounced. Recall that this analysis adds events to the sirukumab group from patients who crossed over or escaped, and the placebo group is depleted of these patients.

Although not conclusive due to the confounding elements of trial design, these analyses suggest that trial design features designed to protect the patients in the placebo group, namely escape and crossover, that depletes

the placebo population of patients with highest disease activity and enriches the sirukumab groups with these high disease activity patients may contribute to the mortality imbalance.

Note -- and this is important -- both we and the FDA have evaluated these same data using other methodologies, for example, Kaplan-Meier analyses, but these are similarly confounded in data beyond week 18.

Since the internal comparisons to placebo are biased by differential crossover, we also determined if these data were consistent or inconsistent with mortality data observed in studies of other approved RA drugs conducted in similar populations with the proviso that cross-study comparisons can also be fraught with confounding variables. We used a program which study patients with moderate to severe RA defined by generally similar criteria and also included escape mechanisms for placebo-treated patients, which may introduce the same biases.

The left-hand panel of this slide, depicting

mortality rates per 100 patient-years in patients treated with active drug, demonstrates that the mortality rates are remarkably consistent across these programs, and the sirukumab data fall within the middle of this data set.

The right-hand panel shows mortality rates among patients treated with placebo in each of these programs. Note that the point estimate for placebo-treated patients in the sirukumab program was lower than that of most other programs. Furthermore, the numbers of events are small and confidence intervals wide and overlapping, suggesting the possibility that chance may account, at least in part, for the difference between sirukumab and placebo.

In evaluating both these data as well as data from the controlled portions of these same RA development programs, we have concluded the sirukumab program is not unique in our mortality observations in numbers of events, rates, or imbalance beyond the true controlled periods of trials.

Together these analyses help give us confidence in the mortality rate observed in the sirukumab program and that it is consistent with rates observed in RA patients treated with other recently approved drugs. Moreover, the lack of additional deaths in patients treated with placebo after the week 18 placebo-controlled period is consistent with escape and crossover of patients with the highest disease activity to sirukumab, leaving the placebo group depleted of high-risk patients.

Wide confidence intervals indicate that imbalances might be due to chance, but this cannot be ruled out based on these data alone. True risks for sirukumab, as with any drug, will require far greater numbers of treated patients followed for longer periods of time, and Dr. Vratsanos will present our plan to accomplish this goal in postmarketing studies.

We conducted additional assessment of non-fatal infections, MACE, and malignancies because these were the most common causes of death.

As noted earlier in the presentation, rates of serious infection were higher in sirukumab-treated patients than placebo, approximately 5 serious infections per 100 patient-years of exposure for sirukumab versus approximately 2 in the placebo-treated group during the 18-week placebo-controlled period. This rate of serious infections remains stable through the data analysis sets, and again, no dose response was observed.

Rates of MACE in each of the trial periods remained low, and the confidence intervals were wide and overlapping. For each MACE case, in addition to the risk carried by moderate to severe RA, most patients with MACE had other identified cardiovascular risk factors. Overall, these MACE rates were consistent with expected rates for the RA population. In the week 52 and SCS data, MACE rates were numerically higher in the 50-milligram group than the 100-milligram group.

To understand this imbalance, we compared baseline cardiovascular risk factors as well as parameters of inflammation and disease activity

between the treatment groups. These data did not reveal imbalances that explained the dose difference in MACE.

We also evaluated whether lipid changes were different between the dose groups. Shown here are the mean changes in lipid parameters on treatment, and no differences in lipid increases were observed, suggesting that differences in lipid changes does not explain the dose difference in MACE.

Overall, the numerical increase in MACE in the 50-milligram group compared to that of the 100-milligram group was not readily explained by baseline or on-treatment cardiovascular risk factors or disease activity parameters, including lipid changes. Overall, MACE rates were consistent with expectations in the RA population and did not suggest an increased risk of MACE with sirukumab.

Malignancy rates were low in each trial period, though it should be noted that early time periods may underrepresent true rates of malignancy because of patient screening, including complete

physical exam, blood work, and chest x-ray, which may screen out patients at risk for developing malignancy in the early trial period.

Because malignancies are events of long latency, we compared the rates of malignancies, other than non-melanoma skin cancers, observed in our trials versus expected rates using data from the SIR database of the National Cancer Institute adjusted for age, gender, and race.

The observed number of malignancies shown in the first row and the expected number of events shown in the second row were used to generate the ratio of observed-to-expected events called the standardized incidence ratio. The ratio of approximately 1 in the sirukumab groups suggest that the observed rate was similar to the rate expected in the general population.

We also evaluated rates of lymphoma, which occurs with greater frequency in patients with RA. There were no lymphomas in the placebo arm and 2 each in the 50- and 100-milligram sirukumab arms. One of these four cases deserves additional

clarification, as it was a case of a patient with lymphadenopathy but was not proven by biopsy. And although the adenopathy resolved after discontinuation of methotrexate and sirukumab, the assessment of the investigator was that of malignant lymphoma.

Including this case, the standardized incidence ratios approximated 3 for each sirukumab group. Overall, our result showing a standardized incidence ratio approximating 1 do not suggest an impact of sirukumab on overall malignancy risks.

The 3-fold higher rate of lymphoma is consistent with the risk of lymphoma associated with RA, which carries approximately 1.75 to 12-fold increased risk relative to the general population, and this observation is also consistent with rates seen in other RA programs.

To gain further insights as to whether or not adverse event rates increased over time, we examined the proportions of patients experiencing any adverse event or infection by 6-month increments in the left panel, and in the right

panel, we evaluated the rates per 100 patient-years of exposure for serious infections, MACE, and malignancy. None of these rates increased over time. Combining these analyses suggested that additional safety concerns did not emerge with increasing duration or cumulative exposure to sirukumab.

Since our BLA was submitted, just over 900 additional patient-years of experience has accrued. As shown on this slide, rates of targeted events remain stable, including mortality, serious infection, MACE, malignancy, and GI perforation rates.

Finally, to further contextualize sirukumab safety, again with the proviso that cross-study comparisons can be confounded, we evaluated sirukumab safety reference against the IL-6 receptor antagonists tocilizumab and sarilumab based on information published in the FDA summary basis of approval for each product. Shown here, the incidence rates of mortality and adverse events of special interest with sirukumab were generally

similar to rates reported with these two agents.

In summary, sirukumab safety was studied in a large phase 3 program with over 5,000 patient-years of follow-up through the safety update, and the main risks include infections, GI perforations, and certain laboratory abnormalities. Malignancy and MACE rates appear to be comparable to expected rates in the RA population.

Safety differences between the 50-milligram and 100-milligram dosing regimens were modest and generally not higher for the 100-milligram group despite the approximate 4-fold higher dosing intensity, with the exception of higher rates of injection-site reactions and small differences in laboratory abnormalities. Moreover, safety as monotherapy or combined with DMARDs and safety in trial subpopulations were similar.

While we cannot exclude the possibility of a mortality difference, the longer term data are confounded by trial features designed to protect patients on placebo, and moreover, we are committed to further characterization of sirukumab safety in

postmarketing studies.

Based on the analyses shown today, we have concluded that sirukumab has an acceptable safety profile, and the data appear to be comparable to the safety data of other agents that target the IL-6 pathway, and the safety event rates fall well within the broader safety parameters of other agents used to treat RA.

With that, I'll thank you for your attention, and I'll turn the podium back to Dr. Vratsanos who will provide some concluding remarks.

Applicant Presentation - George Vratsanos

DR. VRATSANOS: Thank you, Dr. Yeilding.

There are several important questions on benefit-risk that the FDA has asked you to consider, so I'd like to take a few minutes to summarize our conclusions on benefit-risk.

Regarding efficacy, we are recommending the 50-milligram subQ every 4-week regimen for approval because it has clearly demonstrated levels of efficacy. This regimen demonstrated consistent

efficacy in patients who had persistent high-disease activity despite often trying multiple oral DMARDs or biologics. Efficacy was consistently demonstrated in a spectrum of RA patients, ranging from patients with inadequate response to DMARDs, to anti-TNF therapies, and patients unable to take methotrexate or other DMARDs.

It was effective in rigorously-controlled statistical testing and in sensitivity analyses for the primary endpoints even when using very conservative assumptions. Sirukumab demonstrated the ability to modify the course of RA by inhibiting joint damage. This was evident by 6 months and was true for both erosions and cartilage loss.

For patients, the benefits were consistently demonstrated on endpoints that matter to them such as improving physical and mental components of quality of life, reducing pain and fatigue, and improving their ability to perform activities of daily living.

The safety profile of sirukumab is acceptable when considering the seriousness of this disease and its potentially devastating consequences. The safety is consistent with other members of the IL-6 class. The main identified risks are serious infections, gastrointestinal perforations, and certain laboratory abnormalities. These risks can be monitored and managed by rheumatologists.

The rate of malignancy and MACE are comparable to the expected rates in the RA population. And with respect to mortality, the following three points need to be emphasized. First, there's no difference in the 18-week placebo-controlled period. Second evaluation of the week 52 rates are confounded by the early escape at week 18. Third, the rate observed on sirukumab at week 52 is within the expected range of other biologics for RA.

Janssen is committed to conducting a comprehensive postmarketing safety program to characterize the long-term risks. As an

organization, we have a track record of successfully completing postmarketing safety programs for three biologics: Stelara, Simponi, and Remicade. Risk minimization through appropriate product labeling is critical, and we are committed to working with the agency to ensure adequate communication of risks.

We commit to continuing a five-year long-term extension that will provide a total of 8,500 patient-years of experience, and we plan to conduct enhanced pharmacovigilance for serious adverse events of particular concern for biologics such as malignancy. We will also conduct a pregnancy outcomes study given that RA affects predominantly women.

As we noted earlier in our presentation, we commit to conducting a postmarketing safety study with the objective to more fully characterize risks that are difficult to precisely assess in registrational trials. We will discuss with the agency the most appropriate scientific design.

Today we emphasize that RA patients continue

to require new treatment options, especially those patients whose treatments have not meaningfully helped them. Sirukumab demonstrated substantial levels of efficacy in two independent placebo-controlled trials with the efficacy for the proposed regimen of 50 milligrams every 4 weeks, consistent both from a statistical perspective and also highly clinically meaningful.

The adverse events observed were consistent with the type and frequency of those events seen in RA patients treated with other biologics, including the IL-6 inhibitors. And as you heard from Dr. Schwartzman, rheumatologists are accustomed to monitoring and managing these risks.

The benefit-risk is appropriate for patients with such a serious disabling and potentially crippling disease. Recognizing that pivotal trials cannot adequately characterize some risk, we are committed to conducting a postmarketing safety program, including a postmarketing safety study.

Given the favorable benefit-risk, as a reminder, we're seeking approval for the following

indication: the treatment of adult patients with moderately to severely active RA who have had an inadequate response or are intolerant to one or more disease-modifying antirheumatic drugs.

On behalf of our companies, thank you for your attention and consideration. This concludes our presentation. We'll be happy to address any questions you may have.

Clarifying Questions

DR. SOLOMON: Well, thank you very much. We now have some time for clarifying questions for the applicant. Let's start with Erica.

DR. BRITTAIN: I have a question about slide 86.

DR. VRATSANOS: Slide up, please.

DR. BRITTAIN: I really like the three groupings here, the three ways you're looking at the comparison. I would prefer a Kaplan-Meier format because this is sort of -- this display is most helpful if death is constant over time. But still, it's a very helpful display.

You made a big point about the difference in

risk over time with the non-intent-to-treat groups, and I fully appreciate that. What I wasn't sure is if you actually had looked at your data to see if the placebo patients who did escape because they had more disease activity, if they actually had a death rate that was different -- once they crossed over to drug, that was different than the full group of patients on drug.

DR. VRATSANOS: I'm going to call Dr. Yeilding to the podium. I first wanted to reassure the committee that as a company, we took this issue very seriously and presented I believe a very thorough set of analyses to address this question. Dr. Yeilding can address your specific question.

DR. YEILDING: Newman Yeilding, Janssen clinical development. We did conduct that analysis, and in fact -- slide up -- the patients that do cross over or escape do have a higher mortality rate than the patients that either remain on placebo or the patients that were originally randomized, and that's shown on this panel.

What we've done here is to take those patients who escaped or crossed over, and we looked at the mortality rate in those patients. And you can see here that their mortality rate was -- and this is a total of 5 events, but their mortality rate was about 3- to 4-fold higher than the patients that were originally randomized.

So that is consistent, as you point out, with the expectation that patients with the higher inflammatory burden may have a higher mortality rate.

DR. SOLOMON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Thank you for your presentation. My first question was actually your question on whether the escape patients had mortality rates that were higher or not.

My second question relates to the adalimumab trial. You presented the 52-weeks results, and there was a signal on infection. I was wondering if there was a follow-up to that trial and what happened to the infection rates, or if it stopped at 52 weeks and you didn't follow up the two groups

any longer.

DR. VRATSANOS: The file concluded at week 52.

DR. SOLOMON: Diane? Ms. Aronson?

MS. ARONSON: My question is related to study design. It's two-part. The first is related to the demographics. In the briefing booklet, I believe it's figure 20.

Do you have that slide?

DR. VRATSANOS: We can find that for you momentarily.

(Pause.)

MS. ARONSON: Demographics? Do you have that?

DR. VRATSANOS: Yes. We'll pull it up. It's just taking a while to retrieve the slide.

MS. ARONSON: Okay.

DR. VRATSANOS: Slide up, please.

MS. ARONSON: I wanted to focus particularly on the race aspect of the small number of black and African Americans registered for the trial. I tried to find incidence for rheumatoid arthritis in

the different racial populations, and it was a challenge. But I did find some data source, Corrona, in a study of racial and ethnic disparities in disease activities in RA patients, Greenberg, et al. It's on the NIH site.

It does state that African Americans have a lower response and lower clinical rates and functional status. I don't know if I can get an answer to this question, but it's just kind of an observation of -- I wonder about that part of the study design.

The second part of my question is related to exclusion. Could you please list the exclusions in the study?

DR. VRATSANOS: Surely. Regarding the first part of your question, you do point out that we had relatively small numbers of African American patients in our trial. It's hard to read from the slide, but there were 5, 7, and 5 patients across the three treatment groups of responders. We can't of course make definitive conclusions. What we can say is that it's trending in the right direction

with respect to that, with that population.

With respect to exclusion criteria, they were fairly typical for phase 3 randomized trials. We excluded patients with serious or potentially progressive systemic disease who would not be good candidates for a clinical trial.

MS. ARONSON: Do you have a slide on that, please?

DR. VRATSANOS: We can find that for you momentarily.

(Pause.)

DR. VRATSANOS: It should take a few more moments; that's all.

We will try to get you that information with the specific exclusion criteria across the trials after the break if possible. We don't have it ready at this time.

DR. SOLOMON: Did you have a specific question about criteria?

MS. ARONSON: Yes, I do. With all the exclusions, and then the markers of adverse events, I guess as a patient, I want a level playing field

of that recognition of what wasn't included, like I don't know if I have an opportunistic infection in my body; or if there were exclusions that just show -- and the results are like 3 percent, but those patients weren't studied. That's what I try to wrap my head around, how as a patient do I make that choice knowing if I might have that as a history but don't yet now. Because of my disease, how do I evaluate that. So that's what I'm trying to -- I would have liked to have seen a list.

I saw in the briefing booklet some, but it would be good to know because I don't believe on a label it says patients not studied in this trial. So, thanks.

DR. VRATSANOS: Is the question specifically with respect to infection or is it more broad than that?

MS. ARONSON: It's broader than that, but infection is real important.

DR. VRATSANOS: So before we can find the slide, what we can share, again, as is typical in phase 3 trials, patients with a recent history of a

serious infection or, of course, an ongoing infection would be excluded, again, for patient safety.

DR. SOLOMON: Jennifer?

DR. HORONJEFF: Thank you for the presentation. I want to say, from the consumer standpoint and because I'm interested in patient-centered outcomes, that I appreciate that not only did you study more quality-of-life measures but that you actually presented them here. I think that's very important.

You presented the relationship of what you found in your current study with the mortality and adverse reactions or adverse events in other biologics. I'm curious if you looked at those same sort of relationships with quality-of-life measures, with SF-36, or anything else, that we can be able to see if there's any difference between what you were looking at and what we know of other biologics.

DR. VRATSANOS: Just to make sure I understand your question, you're asking about

comparison on some of the PROs with other biologics. Is that correct?

DR. HORONJEFF: Yes, exactly.

DR. VRATSANOS: What we can present is the study results from 3005, which compared sirukumab to adalimumab. That's the only trial we have with the direct comparison, and there we will find the data as soon as possible. What you can see is that there were very comparable improvements in the SF-36 and in the FACIT between both doses of sirukumab and adalimumab.

DR. HORONJEFF: So you say you did measure that in the adalimumab study.

DR. VRATSANOS: Yes, we did.

DR. HORONJEFF: Okay. And what you had as study 2 and 3, those didn't have any comparator to another biologic. So that's the only data that I saw presented that you looked at that.

DR. VRATSANOS: Slide up, please. We can show you the data, surely.

DR. HORONJEFF: Thank you very much.

DR. VRATSANOS: This is study 3005. So this

is monotherapy; as a reminder, 3 arms, the 50-milligram regimen in pink, 100 in purple, and adalimumab 40 milligrams every 2 weeks in blue, looking at the same outcome, which is proportion of patients with improvement of more than 5 units clinically meaningful, very consistent results across the groups.

DR. HORONJEFF: Thank you for sharing that.

DR. VRATSANOS: Slide down, please.

DR. SOLOMON: Dr. Felson?

DR. FELSON: Yes. I also want to appreciate the sponsor's comprehensive presentation of data. I thought it was very nice. I have a question for you about expected mortality rates and adverse event rates in people with worse disease versus milder disease because one of the crux's of your argument was that when you switch people off of placebo, they had worse disease and therefore would have a higher expected mortality and adverse event rates.

I think in the rheumatology community, we all accept that relationship, but I'm not sure it's

a very strong relationship. And I guess I want to ask you if you know the numbers there. What you saw was a 4-fold increase in mortality in that group switched. And the question is, is that really the expected difference in mortality between those with bad disease and those with milder disease? I'm pretty sure it's not.

So the question is, what is the expected difference there?

DR. VRATSANOS: I'm going to invite Dr. Yeilding to address your question.

DR. YEILDING: Newman Yeilding, Janssen clinical development. So we actually did look at the literature -- and you can bring this slide up, please -- to see what are the hazard ratios that are associated with different levels of disease activity. And this has been recently well studied, so you can see in the first bullet in the RABBIT registry an association between DAS28 and hazard ratios were observed. With patients with severe disease, that's DAS28 of greater than 5.1 having a hazard ratio of about 2 and half -- 2.4-fold

greater than patients with a DAS28 of less than 3.2.

The National Data Bank for Rheumatic Diseases suggested that HAQ-DI is the strongest predictor of mortality with 1 standard deviation of change increasing the odds ratio for mortality about 2.3-fold. And then the Norfolk Arthritis Registry has also quantitated association of HAQ per unit of change with a hazard ratio of approximately 1.4 to 1.5.

In terms of the -- you noted that in our data there was about a 4-fold difference in those event rates. I will also note that the confidence intervals around those point estimates were quite wide and the numbers of events is very low. I would not want you to conclude that that is the true relative difference because of the small numbers of events that we're looking at.

DR. SOLOMON: Dr. Becker?

DR. BECKER: Hi. This is Mara Becker. I was interested in your phase 2 trial, that divergence that we saw by week 24 between the two

dosing intervals that were studied with the trend of the 50-milligram dosing actually looking like it was going down. And I was curious if you had any clinical efficacy data beyond the week 24 that you can present or share with us, in the trials.

DR. VRATSANOS: That was the last dose, so then patients were followed for safety off drug for a while. So that was the last dose.

DR. BECKER: I mean in the 3002 and 3003 trials, the longer term trials. You denote efficacy.

DR. VRATSANOS: Oh, surely. We can show you in the pivotal trials efficacy out to 52 weeks from study 3002. We can show you the primary endpoint. And what you'll see in a few moments is that efficacy was very strongly maintained over the entire 1-year period.

While we pull that up, I can also share we looked at the data in a different way, which is to ask the question, if you had a response early on in that trial, week 16, what was the likelihood you would maintain that response out to week 52? And

the answer is across the spectrum of endpoints we measured, it was over 75 to 85 percent. So patients were highly likely to maintain their response if they had a response early on.

Slide up, please. This is at the group level, the results from study 3002. Time out to 52 weeks is on the X-axis, placebo is the dashed line, and then it's hard to see of course because the two dose groups are overlapping in terms of the response over time. So that difference from placebo was maintained out to 52 weeks.

DR. BECKER: Thank you.

DR. SOLOMON: Dr. Weisman?

DR. WEISMAN: I'd like to ask you to speculate a little bit since there are biologic differences between blocking the receptor and blocking the cytokine itself. What do you expect the safety considerations to be, the same or different, from our previous experience with the other IL-6 blockers?

DR. VRATSANOS: I'm going to invite Dr. Elloso to comment on the differences between

targeting the receptor versus the ligand. Of course, as you mentioned, what we can say is just based on the clinical data that we have to date, which looks very similar to the other IL-6 members of the class.

DR. ELLOSO: Good morning. Merle Elloso from Janssen immunology discovery research. As Dr. Vratsanos had detailed in the beginning of his talk, like the IL-6 receptor antagonist, sirukumab prevents the binding of IL-6 to both forms of the receptor, thereby inhibiting both classic and transient link. So with respect to inhibiting the IL-6 pathway, the impact would be similar between the two approaches.

With regard to the differences, we explored several hypotheses. For example, generally speaking, by targeting the cytokine with a monoclonal antibody, you would potentially decrease the risk of cellular lysis as compared to targeting and then -- cellular surface receptor with a monoclonal antibody.

More specific to rheumatoid

arthritis -- slide up, please -- we know that there's less circulating cytokine in RA, which could translate to higher target coverage with lower dosing requirement. And this is because the levels of soluble IL-6 receptor has been shown to exceed those of IL-6 by at least 100- to 1,000-fold, which suggests that more drug would be required to neutralize the soluble IL-6 receptor, and that's in addition to targeting cell-surface receptor.

So what we observed, as noted on the right side, is that we see -- and as mentioned earlier -- as linear PK, which supports dosing once monthly. And as the biology of the IL-6 pathway has evolved, additional considerations were further explored. The second relates to specificity. As you heard earlier, there are alternative ligands that have been identified that bind to both forms of IL-6 receptor, namely ciliary neurotrophic factor, or CNF, and p28.

As Dr. Vratsanos had noted earlier, the biological significance of these alternative

ligands and their signaling, as well as the relevance to RA, is really not understood at this time. But what we do know, based on published studies, is that the anti-6 receptor antibodies, including tocilizumab, can inhibit cellular responses induced by these ligands. So while both approaches have overlapping mechanisms of action, by targeting the cytokine, we inhibit the pathway with more selective inhibition of IL-6.

Lastly, what's been reported recently is that a polymorphism within the IL-6 receptor gene results in increases in soluble IL-6 receptor. We know, based on this published finding, that this impacts the responsiveness to tocilizumab, so we've actually looked at these polymorphisms and have also concluded that they are associated with increased levels of soluble IL-6 receptor. But in contrast, it does not impact the efficacy of sirukumab.

DR. SOLOMON: While you're there, let me just ask to follow up. So is there a novel mechanism? How should we think about this? Is it

a novel mechanism or not? Because that was mentioned several times, and I'm still a bit unclear.

DR. ELLOSO: Well, as I mentioned earlier, it has an overlapping mechanism of action as the IL-6 receptor antibody. So the impact on the IL-6 pathway per se is similar, but with the added benefit, potential benefit, of selective targeting of IL-6. So I would say that it's similar but with distinct features.

DR. SOLOMON: Dr. Meisel?

DR. MEISEL: Steve Meisel. I've got three questions. I think they'll all be brief. First of all, slide 49, if you can call that up --

DR. VRATSANOS: Slide up.

DR. MEISEL: -- on the right-hand graph, those are the patients who failed anti-TNFs and other biologicals. Am I correct to assume that none of the other two IL-6 drugs are included in that? So you have no comparisons or speculation as to whether this drug would be more or less effective than the other IL-6 agents?

DR. VRATSANOS: So this trial wasn't designed of course to compare --

DR. MEISEL: Right.

DR. VRATSANOS: -- this drug to other IL-6s. Let me clarify. The patients in this trial on other biologics were not failures. They had tried other therapies and discontinued, but for reasons other than lack of efficacy. And indeed, we can show you the data. There was a sizeable number of patients over 100 who had tried tocilizumab. Again, they had not failed tocilizumab. And we looked at the efficacy in that subgroup who had tried tocilizumab.

Slide up, please. In 3002, as I mentioned, that trial also included potentially patients who had tried other biologics, as well as, of course, the trial you're referencing; odds ratios for the primary endpoint. And you can see the data represented by prior tocilizumab, yes, 128 in study 3002, versus no, 1542. So it's somewhere about 10 percent of the population. And overall, what you can say is that there is consistent transfer

efficacy in patients who had tried tocilizumab previously.

DR. MEISEL: Thank you. The second question -- and it's in your briefing book, and I see it in a number of places. But if you just call up table 10 in the briefing document as illustrative.

DR. VRATSANOS: In our briefing document?

DR. MEISEL: Pardon me?

DR. VRATSANOS: In our briefing book?

DR. MEISEL: Yes.

DR. VRATSANOS: Sure. Slide up, please.

DR. MEISEL: This is one of many tables like this. If I look at patients in response, clearly your drug is better than placebo, but there is a very large placebo effect, 40-45 percent, 37 percent in some of the other tables, as high as 50 percent.

Could you comment on the placebo effect that we're seeing, really, all throughout 3002 and 3003?

DR. VRATSANOS: You point out correctly that there is a high placebo response in RA trials. I'm

going to ask Dr. Schwarztman to provide a clinical perspective on this high placebo response across different trials in rheumatoid arthritis.

DR. SCHWARTZMAN: To be clear, though, the way that I would give you a perspective is that the placebo response rates in the ACR20s, 50s, and 70s, for example, are not exaggerated in this program. These are the types of placebo response rates that we have in general in clinical trials.

With regards to fatigue -- and I think you're pointing out this because this is the most exaggerated example of that -- I think that this is still an area that we're learning about, and that the placebo response in general in patients who are in double-blind, randomized studies, who are anticipating that they're receiving drug, may be a bit higher. But to be honest, I think that although you're making it more encompassing by including the other outcome measures, this is the one where it seems to be more exaggerated.

DR. MEISEL: These are patients that you put in here who basically failed other agents, right?

DR. VRATSANOS: Yes.

DR. MEISEL: But you still have this large placebo effect.

DR. VRATSANOS: I think, as Dr. Schwartzman noted, this is a relatively new instrument, it has been validated, and we're still understanding how it performs in clinical trials.

DR. MEISEL: But it's not just FACIT. I mean, it's in the SF-36 and some of the other outcome measures as well.

DR. VRATSANOS: Again, I would emphasize what Dr. Schwartzman did, is that there are high placebo responses in our trials. They're very consistent with what you see in the other trials as well.

DR. MEISEL: Thank you.

DR. SOLOMON: Michael, did you have one more question, and then I have a final, and then we're going to break.

DR. WEISMAN: Just a follow-up to your question that was asked, Dan, are there any risk factors for benefit in your assessment of

biomarkers that you've identified where patients might respond better to this drug as opposed to either the receptor blocker or other biologic drugs? What's been your experience and what do you speculate?

DR. VRATSANOS: I won't speculate. I'll answer with facts. This company was very determined to try to find markers of response, and we did a very exhaustive search with a dedicated team for many months looking at genomics, looking at transcriptome, looking at protein markers. And unfortunately, like other companies, we could not identify a reliable marker or markers of response or even of certain safety events.

So we're left with a program that, unfortunately, we don't have any specific markers of response. We did try very intensely to identify them.

DR. SOLOMON: Last question, then we're going to break. This refers to slide 96, which was malignancies. I just want you to expound a bit on what we see because you're showing us SIRs that

would suggest that the risk with sirukumab is no different than population risks, but we're seeing rates in the sirukumab arm quite different than placebo arm.

I'm -- I think as most of us, we're trying to puzzle over this issue. So perhaps you can walk us through this and maybe expound a bit more.

DR. VRATSANOS: Dr. Yeilding?

DR. YEILDING: Newman Yeilding, Janssen clinical development. What you're noting here, I'm going to just tell you what's in each of the columns first. So what's in the placebo column is obviously just the placebo exposures, and then what's in the other columns are exposures to the entire data set that we have through the SCS cutoff.

What I was trying to convey in my talk was that, especially with malignancies, which are events of long latency, when you only have short follow-up, then the bias will always be against placebo. So if you look in the 18-week placebo-controlled period, there is no imbalance in

malignancy. It's only after that. And that's because -- and this is not unique to the sirukumab program; this is a fairly common phenomenon across clinical trials in rheumatoid arthritis where you have to get patients off of placebo within a reasonable period of time.

So that is our interpretation of the data, and I think that that's borne out by, supported by, observations across the trials as well.

DR. SOLOMON: Great. Well, thank you very much. I think we'll break now for about 15 minutes and be back in the room at 10:25. Thanks.

(Whereupon, at 10:10 a.m., a recess was taken.)

DR. SOLOMON: We're now going to proceed with the FDA presentations.

FDA Presentation - Mark Borigini

DR. BORIGINI: Good morning. My name is Mark Borigini. I'm a rheumatologist and a clinical reviewer in the Division of Pulmonary Allergy and Rheumatology Products. I will be providing a clinical overview of the RA development program for

BLA 761057 for sirukumab.

The subsequent presentations today will include talks on dose-selection considerations by Dr. Pisal; statistical considerations on efficacy by Dr. Koh; and I will finish with a review of safety and risk-benefit considerations, but first an introduction and clinical overview.

As discussed by Dr. Maynard, we will be discussing Janssen's sirukumab licensing application. This slide provides an overview of Janssen's clinical program. Dr. Pisal and Dr. Koh will provide additional details regarding the designs of these studies. Study C1377T04 was a two-part phase 2 study. Studies 3002 and 3003 were placebo-controlled phase 3 studies.

Additional phase 3 data are available from study 3005, which compared 2 doses of sirukumab to an active comparator, adalimumab. Long-term safety data are available from 3004, which was a long-term extension of 3002 and 3003. Study 3001 was an additional safety study performed in Japan.

One of the issues the committee will be

considering is the design of the 52-week placebo-controlled radiographic study 3002. We would like your feedback on this study design for assessment of radiographic progression in rheumatoid arthritis.

Given the availability of multiple approved rheumatoid arthritis therapies and the early and aggressive treatment of RA, it has become challenging to perform placebo-controlled trials of long duration to evaluate radiographic progression in rheumatoid arthritis. Since we are bringing this application to an AC meeting, we wanted to take this opportunity to seek feedback on the design of this study.

The following are some design elements you may want to consider in your discussion, including trial duration, as there was some concern regarding the duration of the placebo-controlled period of study 3002, comparator, and escape options. You will be hearing more about the design and results of the radiographic study in the application in Dr. Koh's presentation. One of the common design

elements in these trials are escape criteria for patients to change therapy if they are not responding.

Study 3002 was placebo controlled for 52 weeks and 3003 was placebo controlled for 24 weeks. In both studies, patients could continue certain background medications such as methotrexate. In both studies, patients who met escape criteria at week 18 were re-randomized to one of the two sirukumab doses evaluated, namely 50-milligram q4 weeks or 100 milligrams every 2 weeks. In 3002, patients who met escape criteria at week 40, an additional late escape to their early escape of week 18, were re-randomized to one of the two doses of sirukumab evaluated.

The escape criteria required less than 20 percent improvement from baseline in both swollen and tender joints. Just as we are asking the committee to consider the approach to dosing in Janssen's RA development program, we are asking members to consider the appropriateness of the escape options incorporated into the studies in

this program. After week 28 in 3002 or week 24 in 3003, patients who met those same criteria for escape could have the DMARDs and/or oral corticosteroids initiated or titrated upwards.

I will now transition to consideration of the relevant regulatory history. A pre-IND meeting was held in March of 2008. The design of the proposed two-part phase 2 study was discussed. Janssen was advised that during drug development, they would need to develop evidence to support the choice of a dose. The IND was submitted in June of 2008 and allowed to proceed.

An end-of-phase-2 meeting was held in April of 2011. At that time, the FDA expressed concerns regarding Janssen's proposal to evaluate a dose in phase 3 -- and at that time, it was 50 milligrams -- that had not been evaluated in phase 2. FDA suggested additional dose ranging or utilizing a dose evaluated in phase 2. Janssen subsequently chose to evaluate doses in phase 3 that had indeed been evaluated in phase 2.

In an information request dated October

2012, the FDA expressed concerns with the design of study 3002. The ethical concern expressed at that time was that patients could remain on placebo for up to 52 weeks. Janssen was instructed to amend the protocol so that all patients randomized to placebo were switched to active treatment at an earlier time point. FDA noted that the selected doses for phase 3 studies -- 100 milligrams every 2 weeks and 50 milligrams every 4 weeks -- were acceptable and at Janssen's discretion.

In a follow-up response dated November 21, 2012, to Janssen's questions regarding whether the rescue mechanisms were adequate for a 52-week placebo-controlled period in study 3002, FDA responded that the protocol was generally acceptable.

Another issue for consideration is the dose selection for the phase 3 sirukumab studies and whether the committee has additional recommendations regarding the approach to such dose selection. So now, Dr. Pisal will provide an overview of the phase 2 data that was utilized to

select doses for phase 3.

FDA Presentation – Dipak Pisal

DR. PISAL: Thank you so much, Dr. Borigini.

Good morning, everyone. My name is Dipak Pisal, and I will present the results of the phase 2 study, which were considered for the dose selection for the sirukumab phase 3 program. Here is the brief outline of my talk. First I'll provide background on what is the agency's general expectations from phase 2 trials in rheumatoid arthritis, then we will discuss the phase 2 study design for sirukumab in the current program and further discuss the efficacy and safety results from that phase 2 study.

Further, we'll discuss the dose selected by Janssen for the phase 3 trial and high-level details about the end of phase 2 interactions between Janssen and the FDA. Finally, I'll conclude with the summary.

In terms of dose selection, the agency's expectation is that there will be adequate dose ranging in the clinical development program and are

explained in the draft guidance. This is especially important in rheumatoid arthritis where many drug products intended to treat RA have the potential to cause dose-related adversity actions due to immunosuppression effects such as infections and other side effects such as malignancy and lipid elevations.

Further, it is an important consideration when optimizing the risk-benefit profile in the setting where there are multiple therapeutic options available to patients. In general, phase 3 dose selection should be based on pharmacokinetic, pharmacodynamic, efficacy, and safety considerations from earlier phase dose-ranging studies and should include a wide range of doses and dosing regimens.

In general, the endpoint used in dose-ranging studies should be consistent with the efficacy endpoint that will be used in phase 3 studies known to be predictive of efficacy endpoints.

In the current application, the proposed

recommended dose of 50 milligrams every 4 weeks and in the phase 3 program, doses of 50 milligrams every 4 weeks and 100 milligram every 2 weeks were evaluated, which were selected by Janssen based on phase 2B dose-ranging study.

Let's take a look at the dose-ranging study. Janssen conducted a phase 2 study, which was a two-part study. Part A was proof of concept study and part B was a dose-ranging study to evaluate efficacy and safety of multiple doses of sirukumab administered by subcutaneous route in patients with active rheumatoid arthritis despite of methotrexate therapy.

In part A, 36 patients were randomly assigned to receive either sirukumab 100 milligram as subcutaneous injections every 2 weeks or placebo through week 10. At week 12, patients randomized to sirukumab were to receive placebo, and patients randomized to placebo were to receive sirukumab 100-milligram subcutaneous injections every 2 weeks through week 22.

The major efficacy endpoints in part A were

the change from baseline in DAS28 CRP at week 12 and ACR50 responses at week 12. In part B, 151 patients were randomly assigned to receive subcutaneous injections of placebo or 4 different sirukumab doses for a 24-week blinded dosing period.

The proposed sirukumab doses tested were at 100 milligram every 2 weeks, 100 milligram every 4 weeks, 50 milligram every 4 weeks, and 25 milligram every 4 weeks. At week 12, patients randomized to the placebo group were to receive sirukumab 100 milligrams subcutaneous injections every 2 weeks through week 24. The primary endpoint in part B was ACR50 responses at week 12. The efficacy and safety data were collected, even after the last dose, for up to week 38.

This slide shows the ACR20, ACR50, and ACR70 responses up to week 12. If we see ACR50 responses, which was the primary endpoint in part B of this clinical trial, we can see a higher proportion of patients achieved ACR50 responses at week 12 in each of the 4 sirukumab treatment groups

compared with the placebo. The 100-milligram every 2 weeks and 50-milligram every 4 weeks treatment group showed a higher response as compared to other treatment groups.

This slide shows the longitudinal plots for ACR scores. The left-hand side figure shows the results for ACR20 responses, and the figure on the right-hand side shows the ACR50 responses. The Y-axis is shown as proportion of subjects achieving ACR20 or ACR50 responses shown at 0 to 100 percent in these figures, whereas the X-axis shows the visits from week 0 to week 24.

The placebo response is shown as a pink-colored dashed line and circles. The 25-milligram every 4 weeks dose group is shown by blue; 50-milligram every 4 weeks dose group is shown by green; 100-milligram every 4 weeks dose group is shown by lime green; and 100-milligram every 2 weeks dose group is shown by an orange color.

A similar color scheme has been used for figures on the next slide. We can see a higher proportion of patients achieved ACR responses at

week 12 in each of the 4 sirukumab treatment groups compared with the placebo group. Overall, the 100-milligram dose group showed the trend of higher response as compared to the lower-dose groups.

Now let's take a look at the continuous endpoint, one of which is disease-active score 28 C-reactive protein, referred as DAS28 CRP score henceforth. The continuous endpoints are generally sensitive than dichotomous endpoints. The left-hand side figure shows the mean DAS28 CRP scores from week 0 to week 24. In general, DAS28 score between 2.6 and 3.2 represents low disease activity, whereas scores between 3.2 and 5.1 represent moderate disease activity, which are shown by horizontal reference lines in this figure.

All treatment groups showed a higher response than placebo. We can see that the highest dose group, which was 100 milligrams every 2 weeks, showed maximum efficacy and showed separation than the lower doses at later time points from week 12 to week 24. The right-hand side figure shows a mean change from baseline for DAS28 score up to

week 24. A trend of separation in mean change from baseline DAS28 CRP between sirukumab treatment groups at later time points was observed.

Similarly, if we look at the clinical disease activity index scores, referred as CDAI scores henceforth in the presentation, it is similar DAS28 CRP scores but does not include CRP. The left-hand side figure shows the CDAI scores from week 0 to week 24. CDAI scores between 10 and 22 represent moderate disease activity and more than 22 represents high disease activity, which are shown by a horizontal reference line in this figure.

All treatment groups showed higher response than placebo. The highest dose group, which was 100 milligrams every 2 weeks, showed maximum efficacy and showed separation than the lower doses, which were 25 milligrams every 4 weeks, 50 milligrams every 4 weeks, and 100 milligrams every 4 weeks, from week 12 to week 24. The right-hand side figure shows the mean change from baseline for CDAI score up to week 24. A trend of

separation in mean change from baseline CDAI scores between sirukumab treatment groups was observed at later time points although no dose-response relationship was observed for CDAI up to week 12.

To summarize efficacy, we can say that, in general, all sirukumab dose groups showed better response than placebo. There was a trend showing higher efficacy with higher dose towards the later time points, although no dose response was observed after week 12. In case of ACR20 and ACR50, the 100-milligram dose group showed a trend of higher response.

If we look at the continuous endpoints, there was a clear separation between treatment groups in case of mean change from baseline DAS28 CRP and CDAI; no clear separation in mean DAS28 CRP and CDAI scores, except the 100-milligram every 2 weeks dose group, which showed maximum efficacy as compared to the other doses.

So looking at this data selection of 100 milligrams every 2 weeks and 50 milligrams every 4 weeks, which is 4 times lower, were a

reasonable choice to carry forward for phase 3. However, it should be noted that this is a small study with a sample size of around 30 subjects in each treatment group.

Now if we look at the safety results from lab values, we can see the neutrophil count, platelet count, hemoglobin, leukocyte count, and liver enzymes, such as AST and ALT, showed a larger magnitude of change in all treatment groups than placebo. This table shows a mean change from baseline at week 12 in different lab values across all the dose groups. If we compare the placebo response with the sirukumab treatment group, we can see all the lab values showed a larger magnitude of change for sirukumab treatment groups than placebo.

Another point, which is not shown on the slide and shown by Janssen earlier, is that changes in CRP levels. All the sirukumab treatment groups showed a significant decrease in CRP levels than placebo. To summarize the lab results, it appears that no clear dose responses are observed, but all treatment groups showed a larger magnitude of

change than placebo.

Based on the efficacy and safety data, exposure response modeling, which involved efficacy analysis and PK ACR20 exposure response model, Janssen initially proposed following dosing regimens at the end of the phase 2 meeting. These doses were 100 milligram every 2 weeks, 50 milligrams every 4 weeks, and 50 milligrams every 12 weeks. The last dose, 50 milligrams every 12 weeks, was not studied in the phase 2 study; hence, was discussed at the end of the phase 2 meeting.

At the end of the phase 2 meeting, based on the data provided at the end of the phase 2 meeting package, the FDA expressed concern about the lack of clinical data in support of the 50-milligram every 12-week dose group for sirukumab, as the 50-milligram every 12-week dose group was not studied in the current phase 2 program.

The FDA mentioned that Janssen may have a good reason to consider a 50-milligram every 12-week dose to move forward so Janssen can either

do an additional dose-ranging study to evaluate lower doses and/or come up with alternative dose utilized every 2 weeks, or an every 4-week dosing regiment as it was evaluated in the current phase 2 trial.

As mentioned by Dr. Borigini earlier, in a follow-up communication with Janssen, the FDA said that selected doses for phase 3 studies, which was 100 milligrams every 2 weeks and 50 milligrams every 4 weeks, were acceptable and at Janssen's discretion, but concerns raised at the end of the phase 2 meeting were noted and referred to.

To summarize phase 2 dose-study results for efficacy and safety, we can say that all sirukumab dose groups showed better response than placebo. There was a trend of higher efficacy with higher doses at later time points. No dose response was observed up to week 12. In case of safety results, no dose response was observed for safety lab values, however, all sirukumab treatment groups showed a larger magnitude of change.

Based on the overall information, Janssen

selected 100 milligrams every 2 weeks and 50 milligrams every 4 weeks as their final doses for the phase 3 studies. During the committee's discussion this afternoon, we'll ask you to consider Janssen's final dose evaluation in phase 3. At this point, I would like to turn the podium to Dr. Koh to discuss the efficacy results from the phase 3 studies.

FDA Presentation - William Koh

DR. KOH: Thank you, Dr. Pisal.

Good morning. My name is William Koh. I am the statistical reviewer for sirukumab. I will be presenting the efficacy results.

Here is an outline of the topics I will cover. I will begin with an overview of the phase 3 efficacy studies. I will describe the important features of these designs. I will present the key efficacy results in the two placebo-controlled studies. I will also present key efficacy results from the active-controlled study. I will then end with conclusions based on the totality of the clinical data from these

studies.

This is the same overview of the clinical development program that was presented by Dr. Borigini. My presentation will focus on the three efficacy studies boxed in red. I will refer to these studies by the last 4 digits of the study name. They are 3002, 3003, and 3005.

This slide describes the design of the three efficacy studies. I will first focus on results from the placebo-controlled studies 3002 and 3003. Study 3002 was a 52-week randomized, double-blind, parallel-group clinical study in 1670 patients with active rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs, or DMARDs, by history and not confirmed further.

In study 3003, this was a 24-week placebo-controlled period and was a randomized, double-blind, parallel-group clinical study in 878 patients. The RA patient population had an inadequate response or are intolerant to anti-TNF agents by history and not confirmed further. In these two studies, patients were randomized in a 1

to 1 to 1 ratio to placebo, sirukumab at 50 milligrams every 4 weeks, or sirukumab at 100 milligrams every 2 weeks.

Study 3002 incorporated an early escape at week 18 and a late escape at week 40. The escape criteria was based on the less than 20 percent improvement from baseline in both swollen and tender joint counts. Placebo patients who met the criteria were re-randomized to either of the sirukumab dosing regimens.

Patients who met escape criteria on the sirukumab dosing regimens remained in their respective randomized groups. At week 28, subjects in all treatment groups who had less than 20 percent improvement from baseline in both swollen and tender joint counts could adjust or initiate DMARDs and/or corticosteroids.

This study had co-primary endpoints of the American College of Rheumatology or ACR20 response at week 16 and the change from baseline in radiographic score at week 52. The study also included a number of secondary signs and symptoms

endpoints evaluated at week 24 with the exception of major clinical response. This endpoint was defined based on the continuous ACR70 response over any 6-month period during the 52-week study.

The design for study 3003 was similar except that the placebo-controlled period was 24 weeks. Like study 3002, the study had escape criteria to re-randomize inadequately responding placebo subjects to the sirukumab arms at week 18. There was a single primary endpoint ACR20 response at week 16.

ACR20 is a common endpoint used in RA clinical trials to evaluate evidence of efficacy for signs and symptoms. ACR20 is a binary responder endpoint defined by achieving at least 20 percent improvement from baseline in the tender and swollen joint counts in addition to at least 20 percent improvement from baseline in 3 of the 5 additional measures of disease signs or symptoms.

In study 3002 and 3003, patients who initiated DMARD treatment, increased methotrexate dose above baseline, initiated use of

corticosteroids for RA, or discontinued study agent injections were considered non-responders for ACR20 and other responder type endpoints.

Patient demographics and anthropometric variables were generally balanced across treatment arms and similar across the two studies. Patients were more frequently female and more frequently white. There was a higher frequency of patients age 65 and above in study 3003.

Now, I will describe the patients' disposition of study 3002. Approximately 93 percent of the patients were on randomized study treatment at week 16. Approximately 84 percent of the patients completed 52 weeks on randomized or escape treatment. The proportion of patients who discontinued prior to week 52 was slightly higher in the placebo group relative to the sirukumab arms.

I will also draw your attention to the number of subjects who remained on the originally randomized treatment at week 52. Forty-nine percent of the placebo subjects remained on placebo

at week 52. This was primarily because approximately 38 percent of the originally randomized placebo subjects escaped to sirukumab arms over 52 weeks.

In study 3003, about 87 percent of the patients remained on randomized study treatment at week 16. Approximately 84 percent of the patients completed 24 weeks on randomized or escape treatment. By week 24, only 56 percent of the placebo patients remained on placebo, and in this study, about a third of the placebo patient escaped to sirukumab arms.

ACR20 was the primary endpoint for both studies 3002 and 3003. In both studies, there was statistically significantly higher probabilities of ACR20 response rates for both dosing regimens of sirukumab compared to placebo. The placebo ACR20 response rates were similar across the two studies.

The ACR20 response rates were numerically lower for both sirukumab doses in study 3003. The estimated treatment effect for the proposed 50-milligram dose was an absolute increase in ACR20

response probability over placebo of 28 percent in study 3002 and 16 percent in study 3003.

We next looked at the trends of ACR20 over the course of the study. In both graphs, the horizontal axis describes the week of study. The vertical axis describes the ACR20 response rates. The solid line with black squares represents the ACR20 trend for the placebo arm. The solid line with circles represents the ACR20 trend for the 50-milligram arm. The solid line with triangles represents the ACR20 trend for the 100-milligram arm.

There are two key observations here. First, we see that there was a large separation between both sirukumab dosing regimens relative to placebo observed across all visit weeks. Second, we do not see a numerical separation between the 2 doses of sirukumab across time.

We also looked at the individual components of ACR20 at week 16 for both studies. These results were based on patients who remained in the study and had observed week 16 data. In

study 3002, we see consistent trends of improvements across all individual components of ACR20 at week 16 in favor of the sirukumab 50 milligrams every 4 weeks and 100 milligrams every 2-dosing regimens relative to placebo.

One important component is HAQ-DI, a measure of functional ability. There was strong evidence of an effect of both sirukumab doses on HAQ-DI in study 3002 as well as in study 3003. Such consistent trends of improvement were also seen in study 3003, although the trend for swollen joint counts comparing sirukumab 50 milligrams every 4 weeks relative to placebo was not as strong. The results for the individual components of ACR were largely similar between the two sirukumab doses with slight trends towards greater improvement on sirukumab 100 milligrams every 2 weeks in study 3003.

In this figure, we show results for selected secondary signs and symptoms endpoints, including ACR50, ACR70, DAS28 less than 2.6, and major clinical response. Results for study 3002 showed

consistent trends of benefit in favor of both sirukumab doses relative to placebo. Similar consistent trends of benefit in favor of the sirukumab doses relative to placebo were also noted in study 3003. The estimated effect sizes were numerically smaller relative to dose observed in study 3002.

This slide shows the result for the SF-36 physical component and mental component in summary scores at week 16. The mean changes from baseline in the SF-36 physical component and mental component summary scores at week 16 in patients treated with sirukumab was statistically significantly greater compared to patients treated with placebo in both studies.

Progression of radiographic structural damage in inflammatory arthritis is an important clinical trial endpoint. The van der Heijde modified Sharp radiographic scoring method was used in study 3002 to assess structural damage. The scoring method grades the presence of erosions in the joints of the hands and feet, and the presence

of joint space narrowing in the hands, wrists, and feet.

The maximum value of this scoring method is 448. The change in vdH-S score at week 52 was a co-primary endpoint in study 3002 and was analyzed using linear regression on normal scores, adjusting for categorical baseline methotrexate use and treatment groups.

The prespecified statistical analysis of the effect of sirukumab on radiographic progression utilized an approach, often termed linear extrapolation, to handle missing data and post-escape data on the placebo arm. The linear extrapolation approach, which has been used in previous RA trials, imputes a single week 52 value in patients who escape or withdraw from the study prior to week 52.

In the applicant's analysis, patient data after early escape on the placebo arm were considered missing, then the applicant feeds [indiscernible] a line through the baseline score and the last observed radiographic score

before early escape and used that line to assign a week 52 value to the patient.

We have some concerns with the linear extrapolation approach. This includes its reliance on the strong and unverifiable assumption of linear progression in the absence of escape and its use of a single imputation approach that does not appropriately account for the statistical uncertainty in the imputation process.

Given these concerns, we considered several supportive analyses to be important. In particular, one key analysis was based on all observed data, including all radiographic data collected from placebo patients who early escaped or late escaped to sirukumab arms and analyzed patients according to their originally assigned treatment arm. Other additional analyses included a mixed effects analysis to more appropriately account for the statistical uncertainty around patients missing radiographic scores.

Results from the prespecified primary analysis or change from baseline in radiographic

score at week 52 are shown here. Higher values of the change from baseline represents a larger degree of radiographic progression. As seen in the red box, there was strong evidence of an effect of both sirukumab doses relative to placebo in inhibiting radiographic progression.

We see that the estimated difference of the change from baseline at week 52, comparing 50 milligrams every 4 weeks to placebo, was negative 3.2 based on the prespecified analysis using linear extrapolation. However, we note that 48 percent of the placebo patients were imputed in this analysis. Thus, we also present supportive analysis using all observed radiographs taken regardless of escape or treatment discontinuation.

Analyses based on all observed data, regardless of escape or treatment discontinuation, also show persuasive evidence of an effect of sirukumab on radiographic progression for both doses at week 52. The estimated treatment effects were slightly smaller in this analysis than the primary analysis. Additional analyses evaluating

the rate of change in vdH-S in the absence of early escape based on a mixed-effects model also supported an effect of sirukumab.

In summary, the totality of the data supports the treatment effect of sirukumab on structural damage progression. The amount of estimated radiographic inhibition was similar for 2 doses of sirukumab. The potential effect of missing data was one of the statistical issues we explored during our review of the efficacy data. The amount of missing data at week 16 was small, ranging from 5 to 8 percent and 12 to 14 percent across arms in studies 3002 and 3003, respectively.

The following endpoints, ACR20 and HAQ-DI at week 16 and vdH-S at week 52, were evaluated based on tipping point analyses. In this sensitivity analyses, we estimated differences between the treatments under varying missing, not at random, assumptions about the unobserved outcomes.

In this analysis, the tipping points -- that is the assumptions under which there was no longer evidence of efficacy -- were generally considered

implausible. Therefore, the various tipping point sensitivity analysis conducted were generally supportive of the efficacy findings for both sirukumab dosing regimens in both studies.

Now I'll move on to discuss the active-controlled study 3005. Study 3005 was a 24-week, randomized active-controlled parallel-group, double-blind study that evaluated the efficacy of sirukumab as a potential monotherapy. Patients in this study had previously failed methotrexate for either safety or efficacy reasons.

In this study, patients were randomized to receive either adalimumab 40 milligrams every other week, sirukumab 50 milligrams every 4 weeks, or sirukumab 100 milligrams every 2 weeks. Patients who had less than 20 percent improvement from baseline in both swollen and tender joint counts were offered early escape in this study at week 16.

Patients on adalimumab who met early escape criteria were uptitrated to 40 milligrams every week dosing. Patients on sirukumab 50 milligrams

every 4 weeks who met early escape criteria were uptitrated to 100 milligrams every 2 weeks dosing. Patients on 100 milligrams every 2 weeks remained on their respective dosing regimen despite meeting escape criteria. The prespecified multiplicity procedure first compared sirukumab 100 milligrams every 2 weeks versus adalimumab with respect to the co-primary endpoints DAS28 ESR at week 24 and ACR50 at week 24.

The next sequential analysis evaluated sirukumab 100 milligrams with respect to additional secondary endpoints and also compared the sirukumab 50-milligram dose to adalimumab with respect to co-primary and secondary endpoints.

In this study, approximately 87 percent of the patients completed the 24-week double-blind period. There were more subjects who were discontinued prior to week 24 from the sirukumab arms relative to the adalimumab arms.

Study 3005 did not meet its primary objective. In this study, the change from baseline in DAS28 ESR at week 24 was statistically

significantly greater for both sirukumab doses compared to adalimumab, however, there was not a significant difference with respect to the co-primary ACR50 endpoint. The probability of ACR50 response on sirukumab was numerically similar to adalimumab.

To further assess the efficacy results from 3005, we look at the individual components of DAS28 ESR and ACR response. In this table, we can observe that the statistical findings for the weighted composite endpoint DAS28 ESR were driven by the large differences in ESR. However, treatment effects on symptomatic endpoint, such as joint counts and patient global assessment, tended to be similar between the sirukumab doses and adalimumab. We see similar findings for the individual components of ACR20 at week 24. The greater effect of sirukumab on acute phase reactants ESR and CRP is expected due to its mechanism of action.

In summary, overall analysis of the ACR and DAS28 components suggested that sirukumab has

greater effects than adalimumab on acute phase reactants. Effects on symptoms and function were largely similar between the products. Thus, there was not evidence of superiority of sirukumab to adalimumab as a potential monotherapy. However, the relatively similar improvements observed on sirukumab and the approved effective active-controlled adalimumab provided additional support for the efficacy of sirukumab.

Now, I'll present the summary of the efficacy findings for sirukumab. In studies 3002 and 3003, there was evidence of a treatment effect for both sirukumab doses on the primary endpoint ACR20 at week 16, and there were notable trends of improvements for all components of ACR20 as well as higher probabilities of other ACR thresholds for both sirukumab dosing regimens.

Additional evaluation based on HAQ-DI and other secondary endpoints were also supportive of the efficacy results. There was also evidence of inhibition of radiographic progression with both sirukumab doses in study 3002 based on the

applicant's prespecified analyses, as well as additional supportive analyses conducted.

Of note, sensitivity analyses indicated that the efficacy results were convincing despite the missing data. Also, we did not see consistent differences in efficacy between the doses of sirukumab evaluated in study 3002 and 3003.

Study 3005 did not provide evidence that sirukumab is superior to adalimumab as a potential monotherapy. However, this study did show generally similar improvements in symptoms and function on sirukumab relative to adalimumab.

With that, I'll hand over the podium to Dr. Borigini to present the safety findings.

FDA Presentation - Mark Borigini

DR. BORIGINI: Now I would like to review the safety and risk-benefit considerations. Once again, a reminder, the primary source of the safety data we will be considering today is from the two phase 3 trials, 3002 and 3003, as well as the long-term extension study associated with these, 3004.

Across the phase 3 studies, 2096 patients were exposed to sirukumab, 1461 of whom were exposed to the sirukumab 50-milligram q4 week dose, Janssen's proposed dose for the treatment of RA. The initial focus of the agency's safety review was the placebo-controlled phase 3 studies, 3002 and 3003, referred to by Janssen as the exposure time controlled analysis set through 18 weeks of exposure, and through 52 weeks of exposure.

The active comparator study 3005 was not included in analyses with 3002 and 3003. This was an active-controlled trial of patients not on methotrexate. Data from 3005 was analyzed through 24 weeks, the so-called adalimumab controlled analysis set, and through the 120-day safety update cutoff date.

The additional safety data included a larger data set, the sirukumab controlled analysis set from studies 3001, 3002, 3003, 3004, and 3005, through 52 weeks to compare the two sirukumab doses, which were included in all of these studies, and evaluate for rare events or events with longer

latency.

This is an overview of the safety of the approved monoclonal antibodies to the IL-6 receptor, tocilizumab and sarilumab. The labeling of both products includes a boxed warning regarding serious infections that may lead to hospitalization and death. Additional warnings and precautions are related to gastrointestinal perforations, laboratory abnormalities, immunosuppression, and hypersensitivity reactions.

You will note that for the IL-6 receptor inhibitors, as well as the other biologic DMARDs approved by the FDA, all-cause mortality is not a warning in their respective labels. Therefore, based on the known safety issues associated with IL-6 inhibition, the focus of this safety discussion will also include deaths; SAEs, serious adverse events; MACE or major adverse cardiovascular events; serious infections; malignancy; GI perforation; lab abnormalities, including neutrophil and platelet count decreases; and lipid and liver function test elevations.

While there is a tendency to compare the mortality in this study with the mortality in the populations studied in other RA development programs, such an endeavor has significant limitations given differences in patient populations, study designs, and analysis methods. It should be emphasized that we are focusing on the data submitted to the agency for its review for this particular product, sirukumab, which as you recall is an IL-6 inhibitor, as opposed to an IL-6 receptor inhibitor.

This table provides an overview of how I will present the safety data. Note that data beyond 52 weeks will not be presented in this table, as the two sirukumab doses studied did not show a separation of any significance for the various safety events analyzed, and you will see that patient-years of exposure will change due to patient censoring.

We are interested in data through 52 weeks because clinical events with long latency such as death and malignancy are relevant in this

application. So the presentation of safety data will include data from studies 3002 and 3003 through 18 weeks. The initial focus of the agency's safety review were these placebo-controlled phase 3 studies through 18 weeks. This is data before escape or crossover, or DMARD, and/or corticosteroid adjustment.

The agency continued to focus on comparisons between those patients originally randomized to the sirukumab 50-milligram and 100-milligram dosages when examining the data through 52 weeks. These comparisons are according to randomized groups.

For all-cause mortality, we will also present the difference of incidence rates in the 95 percent confidence interval to give a sense of the spread or uncertainty surrounding the differences in the point estimates for this randomized population. In addition, we also analyzed results for the sirukumab so-called combined arms that included patients originally randomized to the particular sirukumab doses, as well as patients who crossed over or escape from

placebo to that sirukumab dose.

For patients crossing over or escaping to sirukumab included in the sirukumab combined arms, exposure time began at the time of crossover or escape. The analyses of the combined arms, as you've heard, may be subject to bias given that inadequate responders to placebo who escaped to sirukumab arms and who may be not be representative of those randomized to sirukumab are included in these combined arms.

Moving to the first focus of the safety presentation, we will examine all-cause death in the RA clinical program. All-cause death, we used the cutoff of collecting data for the RA development program, and there were a total of 35 deaths reported. Of these 35 deaths, 34 occurred in sirukumab-treated patients; that is, one was in placebo.

The all-cause deaths listed in this slide are only for patients exposed to sirukumab, and this table does not include the one death on placebo. Patients could have more than one cause

of death as attributed by the investigator. The three major causes of death were major adverse cardiovascular events or MACE, malignancy, and serious infection.

Now we will look at the incidence rates of all-cause death in the placebo-controlled 18-week period and later, after escapes and crossovers have occurred. In the placebo-controlled period, through 18 weeks of exposure, one patient in each treatment group died. In the placebo group, the patient had respiratory distress syndrome. The cause of death in the 50-milligram dose patient was sudden cardiac death, and in the 100-milligram patient, it was myocardial infarction/hypertension. The incidence rate of death was the same in each treatment group as you can see.

In the pooled placebo-controlled control studies 3002 and 3003 through 52 weeks of exposure, the incidence rates of death -- and these are all per 100 patient-years -- were higher in those patients exposed to sirukumab compared to placebo. Compared to the incidence rate of all-cause death

for patients who were initially randomized to sirukumab, the incidence rate of all-cause death was higher for the combined sirukumab 50- and 100-milligram groups.

An imbalance in all-cause death is seen in the through-52-week exposure group when including data after crossover and escape in the analyses. Compared to the incidence rate of all-cause death for patients who were initially randomized to sirukumab, the incidence rate of all-cause death was higher for those in the combined 50-milligram and 100-milligram groups.

An overview of the system organ classes for patients who died as presented in this slide, note that patients could have more than one cause of death attributed by the investigator, as I mentioned before. The main causes of death were related to cardiovascular events, malignancies, and serious infections, including pneumonia, sepsis, cellulitis, and peritonitis.

This slide shows all-cause deaths in the rheumatoid arthritis program by study. Most deaths

occurred in 3002, but deaths also occurred in all other studies except for 3001.

This figure shows a Kaplan-Meier analysis of time to death for studies 3002 and 3003 for the patients in the placebo/sirukumab 50-milligram and sirukumab 100-milligram groups. Of note, the sirukumab groups include data after escape or crossover to sirukumab. You can see the separation between sirukumab and placebo, but the similar curves are for the 2 doses of sirukumab. The two lines are similar, but they separate out from placebo. As we go further down along the X-axis, the small N remaining at that time accounts for the further separation you see out between the doses.

In summary, through 18 weeks of exposure, the incidence rates of all-cause death was higher in each sirukumab group compared to placebo. The three main categories of causes of death were cardiovascular events, malignancy, and infections. A point of discussion is the imbalance of death seen in the sirukumab groups compared to placebo. All-cause death is not included as a warning in the

currently approved IL-6 receptor inhibitor labels.

Next, we will discuss serious adverse events, or SAEs, in the clinical development program. This slide gives an overview of the incidence rate of the SAEs. Again, looking through 18 weeks of exposure, the incidence rate of SAEs was higher in each of the sirukumab treatment groups compared to placebo. During this period, infections were the system organ class in which serious adverse events were most frequently reported, with pneumonia and cellulitis being the most commonly reported SAEs in this class.

Through 52 weeks of exposure, the incidence rate of SAEs remain fairly constant and were similar between the sirukumab 50-milligram and 100-milligram dosages. Through 52 weeks of exposure, infections again were the system organ class in which SAEs were most frequently reported. Similar trends were seen when including data after crossover or escape to sirukumab.

In summary for the SAEs, through 18 and 52 weeks of exposure, the incidence rate of SAEs was

higher in each sirukumab group compared to placebo. Adverse events related to infections were the most frequently reported.

Next, we'll discuss major adverse cardiovascular events or MACE. The agency defined MACE as cardiovascular death, non-fatal MI, and non-fatal stroke, and this will be how MACE is considered in the next several slides that we will look at.

Through 18 weeks of exposure, there were 4 total MACE across the treatment arms, and the incidence rate per 100 patient-years, again, was the same in the placebo and the sirukumab 100-milligram groups, namely 0.3, and higher in the sirukumab 50-milligram group, 0.7.

Similar findings were noted through 52 weeks exposure, again, a higher incidence rate noted in the 50 milligram, and these rates stayed similar when looking at the combined arms, so a persistent higher incidence rate of MACE in the 50 milligrams.

In summary, through 18 and 52 weeks of exposure, the incidence rate of MACE was higher in

the sirukumab 50-milligram group compared to placebo and sirukumab 100-milligram groups. Through 18 and 52 weeks of exposure, the incidence rate of MACE was similar in the 100-milligram group and the placebo group.

Next, we'll look at infections in the program. This overview shows the incidence of serious infections was higher for both sirukumab groups when compared to placebo. Through 18 weeks of exposure, the incidence of serious infections was higher for both sirukumab groups compared to placebo.

The most commonly reported serious infections were pneumonia and cellulitis during this period. There were no opportunistic infections during this 18-week period, but the incidence rate of herpes zoster was higher in both sirukumab groups compared to placebo.

Through 52 weeks of exposure, the incidence rates of serious infection remain higher than placebo for the sirukumab 50-milligram and sirukumab 100-milligram treatment arms. Through 52

weeks of exposure, there was one opportunistic infection in the sirukumab 100-milligram group, and the trends for herpes zoster were similar as those seen through 18 weeks of exposure. There was one opportunistic infection in the sirukumab 50-milligram combined group and 2 opportunistic infections in the sirukumab 100-milligram combined groups in the period observed through 52 weeks of exposure.

In summary for infections, through 18 and 52 weeks of exposure, the incidence rate of SAEs of infection and herpes zoster were higher in each sirukumab group compared to placebo. There were a limited number of cases of tuberculosis and opportunistic infections, but these cases occurred in the sirukumab arms and not in the placebo arms.

The next several slides will discuss the data on malignancy. We will again focus on malignancy, excluding non-melanoma skin cancer in addition to hematologic malignancies in this program.

Through 18 weeks of exposure, there were 2

malignancies, again, excluding non-melanoma skin cancer, observed across treatment arms. Through 52 weeks of exposure, the incidence rate per 100 patient-years of malignancy, excluding non-melanoma skin cancer, was higher, and the same in the 50-milligram and the 100-milligram sirukumab groups compared to placebo. When including data after escape and crossover, this difference was slightly higher in the 100-milligram sirukumab combined group compared to those patients originally randomized to 100 milligrams.

This slide shows the types of malignancy that occurred in studies 3002 and 3003 through 52 weeks of exposure. The malignancy data include non-melanoma skin cancer. The observed followed the pattern of malignancies that would generally be expected in the underlying patient population. Namely, solid tumors such as breast and lung cancer were the most commonly occurring cancer, again excluding non-melanoma skin cancer.

This figure shows the Kaplan-Meier curves for malignancy for the patients in the

placebo/sirukumab 50-milligram and sirukumab 100-milligram groups. Of note, the sirukumab groups include data after escape or crossover to sirukumab. The curves for the two doses of sirukumab are similar, but there is some separation between sirukumab and placebo.

In summary, considering malignancy, through 18 weeks of exposure, the incidence rate of malignancy was the same for the placebo and sirukumab 100-milligram groups and lower for the sirukumab 50-milligram group. Through 52 weeks of exposure, the incidence rate of malignancy was higher in each sirukumab group compared to placebo.

Next, we'll focus on GI perforation in the program. The majority of events of GI perforation were lower GI perforations related to diverticulitis or diverticular perforation. Through 18 weeks of exposure, there were 4 patients with GI perforations, one on 50 milligram sirukumab dose and 3 on 100 milligrams.

Through 52 weeks of exposure, the incidence rates per 100 patient-years remained higher

compared to placebo. When comparing the two doses of sirukumab, the incidence rate of GI perforation was higher for the 100-milligram group compared to the 50-milligram group according to these data. Rates remain slightly higher on sirukumab when including the post-escape or crossover data.

In summary, for GI perforations through 18 and 52 weeks of exposure, the incidence rate of GI perforation was higher in each sirukumab group compared to placebo.

Next, we'll discuss the lab abnormalities looking particularly at lipids, neutrophil and platelet counts, and liver function tests. The mean changes from baseline in LDL, HDL, and triglycerides in studies 3002 and 3003 at week 16 are displayed in this table.

Compared to placebo, a mean increase from baseline in LDL, HDL, and triglycerides was observed in the sirukumab treatment groups. When comparing the two doses of sirukumab, the changes were rather similar. As you can see, at week 16, the mean increase on sirukumab 50 milligrams in LDL

was 21 and triglycerides was 37, and HDL was about 7.

This slide looks at the number of patients with post-baseline values of maximum toxicity grade 1 for neutrophils and platelets through 18 weeks of exposure. It shows that compared to placebo, both doses of sirukumab were associated with a higher proportion of grade 1 decreases in neutrophil and platelet counts.

When comparing the two doses of sirukumab, a similar proportion of patients had grade 1 decreases in neutrophil and platelet counts. The protocols included criteria for permanent discontinuation of study agent due to decreases in neutrophils and platelets. More patients treated with sirukumab than placebo needed to discontinue treatment due to decreases in neutrophil and platelet counts. The criteria for permanent discontinuation was a confirmed neutrophil count of less than 500, and for platelets a confirmed platelet count of less than 50,000.

This table shows the proportion of patients

with toxicity grade 1 abnormalities in AST, ALT, and total bilirubin. A greater proportion of patients in the sirukumab treatment groups -- again, this is through 18 weeks of exposure -- had elevations in AST, ALT, and total bilirubin compared to placebo.

The proportion of patients with these abnormalities was fairly similar with the two doses of sirukumab. Again, the protocols included discontinuation criteria based on abnormalities in liver function tests. And while there were no Hy's law cases, disproportionately more patients on sirukumab were actually withdrawn from the study irregardless of the dose.

In summary, regarding the lab abnormalities seen, sirukumab was associated with increases in lipid parameters and liver function tests and decreases in neutrophil and platelet counts. There was no clear dose response for these lab changes.

Finally, we will review the safety data from the adalimumab comparator study 3005. This slide summarizes the adverse events through the 120-day

safety update cutoff for 3005, and in the next couple of slides, you will see the trend of lab abnormalities through week 24.

Focusing now on this slide, more adverse events of special interest, such as death, malignancy, MACE, and serious infection, are seen with sirukumab. This slide describes the number of patients with post-baseline values for neutrophils, AST, ALT, and total bilirubin of toxicity grade 1 through week 24 in 3005.

We see that sirukumab was associated with greater decreases in neutrophil counts and associated with greater elevations in AST and ALT and bilirubin compared to adalimumab. The proportion of patients with these abnormalities was similar with the two doses of sirukumab. Note again the lack of trending with bilirubin, with AST, and in ALT elevation, again consistent with the experience of the two IL-6 inhibitors on the market.

This slide shows changes in lipid parameters in study 3005, and we see that sirukumab was

associated with greater mean changes in lipid parameters.

In summary, compared to adalimumab, there were more adverse events of special interest such as death, malignancy, MACE, and serious infection with sirukumab. Sirukumab was associated with greater decreases in neutrophil counts and associated with more elevations in AST, ALT, and bilirubin, and greater mean changes in lipid parameters.

In summary, we see imbalances in death, MACE, serious infection, and malignancy in the sirukumab program. The lab abnormalities included lipid elevations, neutropenia, thrombocytopenia, liver function test elevations, and some additional risks included hypersensitivity and GI perforation.

We acknowledge Janssen's plans to utilize a registry analysis study to provide a better understanding of long-term safety concerns related to sirukumab, including all-cause mortality, however, there are significant limitations to this type of study design to address the safety concerns

of interest in this current application.

This slide summarizes the overall risk-benefit, the benefits being that sirukumab, as you've seen, is superior to placebo for signs and symptoms of RA, physical function, and inhibition of radiographic progression in rheumatoid arthritis. The risks include the imbalances noted in death, MACE, and malignancy, serious infection, GI perforation, the lab abnormalities, and hypersensitivity reactions.

That is all I have to say about the safety issues. Thank you.

Clarifying Questions

DR. SOLOMON: Okay. Well, thank you for that presentation.

We now have time for some clarifying questions. Please remember to state your name for the record before you speak. Philip is taking names, so we'll try to keep it in order. Dr. Felson, I think had his hand up first.

DR. FELSON: David Felson. I have a question for the FDA about safety stuff. The

sponsor did a very nice job of presenting comparative data on the safety of this agent versus other biologics. I think there are potentially substantial safety concerns here.

I'm wondering if you had a chance to examine those data, develop data yourself, that look at that question. Is this a new agent whose safety profile is comparable to ones that we already have on the market, or is this something where it's not clear? Is it something where it appears that there are more safety concerns than maybe TNF inhibitors or even other IL-6 inhibitors?

Can you give us a sense of that?

DR. MAYNARD: This is Janet Maynard. As Dr. Borigini mentioned in his presentation, I think there is a natural tendency to say how does this compare to what is available for rheumatoid arthritis. But as he mentioned in his presentation, we really tried to focus on the safety data that was submitted to us in this clinical program because that allows us to do direct comparisons between both sirukumab and

placebo and also between sirukumab and adalimumab.

So we really tried to focus on that data, and I think there is significant limitations if you try and compare event rates across programs.

DR. FELSON: Dan, could I -- sorry.

DR. CHOWDHURY: Dr. Chowdhury here. Can I just add some thoughts to that? Your question is very important, and we actually will be looking for you to discuss this and give us your thinking. We did try and look across programs to see if you could compare and came to some conclusion.

The problem, as you heard, it is very difficult to the extent that it really cannot be done with very vigor conclusions because the designs are different, and the escape criteria are not necessarily all the same. And when the patient escapes, where do they go to? Do they go to the drug? Do they go to the high dose of the drug or do they go to the safety set of the pool, also different?

So it's very different and very difficult to compare, so we did not really go down that path.

And what you saw, really, is the Humira comparative study, which we have, and that doesn't necessarily help much. In that case, we really go back and look across the programs within the program itself, and we make a conclusion for the other IL-6 targeting drugs within the program, did we see any imbalance of mortality, and you heard multiple times we did not. For the TNF blockers, did we see? No, we did not.

To really answer your question, one has to do prospectively designed head-to-head trials, and, really, comparisons across programs are very difficult. Thank you.

DR. SOLOMON: Dr. Brittain?

DR. BRITTAIN: My question is on slide 79, the Kaplan-Meier mortality. So I understand why you compared the groups the way you have. You're comparing the placebos and censoring everybody once they go off drug, and including people on drug who were originally in the placebo group on the drug arm.

Two questions. A, do you have any concerns,

as the sponsor has mentioned, about bias when you do this type of analysis? We know that the groups were not protected by randomization. B, did you do an intent to treat? I understand the intent to treat might dilute the signal, but it seems like one intent to treat that I would like to see with the Kaplan-Meier would censor everybody at the time of the re-randomization, so we are really getting an apples-to-apples comparison.

If the intent to treat curves really line up -- and it will be hard to tell with these small numbers of deaths. But if they really line up, that actually is assuring to me because you would think even though there's going to be some people in the placebo group who've gone on drug, they would have gone on drug later, so you wouldn't expect them to line up perfectly if they were a true effect on mortality.

DR. LEVIN: Yes. This is Greg Levin, FDA. Your first question about the bias, yes, we recognize the concerns expressed by the applicant. We think there is some merit to those concerns. We

put a discussion of that in the briefing document that it is plausible that patients who are escaping from the placebo to sirukumab may represent a higher risk subset.

That being said, there's very limited data through 18 weeks, so we also think there is merit in trying to get as much precision in these comparisons for rare events as possible. So we also think there's merit in trying to utilize this data as best as we possibly can. So we did both analyses, including data through week 52 in which patients were censored, like you said, who escaped and analyses including post-escape data, recognizing the potential limitations but also the increased precision that they provide.

The question you have about the Kaplan-Meier plot, we have it in our briefing document. It's figure 6. I don't have a slide of it, but it's figure 6 in the briefing document, which shows the Kaplan-Meier plot for time to mortality through 52 weeks but censoring patients who escape from placebo to drug rather than including post-escape

data on placebo.

I think that was your question, if you can look at that. Sorry. We don't have a slide of that, figure 6, page 60. Maybe we can call it up. I don't know.

DR. BRITTAIN: In the Kaplan-Meier in figure 6, how are you handling the censoring?

DR. LEVIN: So in this figure, patients who cross over from placebo to sirukumab are censored at the time of crossover. It still includes data through 52 weeks of exposure.

If you're asking for an intention-to-treat analysis where events after -- like a true intention-to-treat analysis where events that occurred after escape are attributed to the placebo arm, we did not do that for these safety risks because I think that would essentially be a comparison between sirukumab and a combined placebo and sirukumab arm that we would be very concerned could mask safety signals, although it does preserve the integrity of randomization. But we did do analyses in which patients were censored at

the time of crossover from placebo to escape, and that's what this is.

DR. BRITTAIN: I totally understand why you did what you did, but I do think there is some merit in doing a pure intent to treat, recognizing any signals would be diluted. Because if there's no difference, that's perhaps a meaningful analysis because you would expect -- I would think you would expect to see a difference that the placebo patients would start dying later.

DR. LEVIN: It's a fair point. I mean, for the intent-to-treat comparisons, we only focus through week 18.

DR. CHOWDHURY: I'm Dr. Chowdhury just to share some talks here. This is a very complicated question, and we do acknowledge the problems that the company raised, you all raised, and we fully acknowledge that. This is a problem with the crossover designs.

You also have to keep in mind, although these crossover designs for the future, because of those reasons, have to be re-thought, in the past,

these were similarly designed studies with crossovers, and we agreed with the safety findings and said these drugs are safe for marketing. And now we are seeing a problem, and we are raising questions about the past where we were okay.

Another thing to keep in mind, which Dr. Felson raised, is to also look in a clinical sense at the patients that crossed over, and then they died. So what really did they die of after crossover? And there were approximately 6 patients also, and of the 6 patients, one had MI -- 2 had MI, 2 had cerebrovascular accident, one had an aneurysm rupture, and one had a road traffic accident.

So you have to put it in the clinical context. As Dr. Felson raised, it was the crossover. Yes, these are sicker patients; how sick they are to die with the next couple of months? Thank you.

DR. SOLOMON: I think Maria is next.

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor. Following up on that, I think it would have been

helpful -- I don't know if that was done or not -- to see the Kaplan-Meier curves for the different subgroups even though the randomization is lost, but how the crossovers behaved as far as Kaplan-Meier and whether they died a week after they were switched over or after 3 or 4 dosages. So I don't know if that was done or not.

My other comment is that once the randomization is broken with the crossovers and all of that, I think it would have been appropriate to do some sort of multivariate analysis where one could adjust for comorbidity and for age because it seems to be that from what the sponsor presented, that a lot of the differences with the placebo is because the placebo appears to be a healthier group than even what we see in the general population with respect to malignancies, for instance, in some of the other groups. So they might have been younger or less comorbidities, I don't know, but I don't think that was accounted for.

My third comment is that all the data that we've seen is pooling the two trials. So to me, it

would be important to know if the two trials were different because if one trial was really carrying all of the effect, then it could more an abnormality than if it's actually the two trials that are showing that excess in mortality.

So I couldn't find that anywhere. I was looking now, and I didn't recall seeing it before. But the effects that we are seeing on the safety signals, the important ones, particularly death, are they consistent across the two trials 02 and 03 -- I think they are -- or is it mostly the effect of a single trial carrying on?

DR. MAYNARD: In terms of the analyses, looking at it by study, if I could bring up FDA slide 78, please. We did look at the number of deaths that occurred in the different studies. We don't specifically have incidence rates and the analyses we've shown today from the different studies, but on this slide, you can see that the majority of the deaths did occur in study 3002.

DR. SUAREZ-ALMAZOR: And is there anything particular about that study that would cause such a

difference in deaths compared to the other one? Have you looked at whether some of these patients may have had more comorbidities, were older, or what not?

DR. MAYNARD: We didn't do specific multivariate analyses to look or to see if there were differences. As we have discussed, the design of the studies was somewhat different, so 3002 was placebo controlled for 52 weeks as compared to 3003, which was placebo controlled for 24 weeks. So there is just a difference in the study design itself, but in terms of the patient population, we don't have a backup slide that has a head-to-head comparison of the different patient populations. The sponsor may have that if they want to show them.

DR. FELSON: This is Dr. Felson again. Can you --

DR. SOLOMON: We have a whole list of people looking for it. I think Sean you're up next.

DR. CURTIS: Hi. Sean Curtis. Regarding the MACE slides -- I think they are 88 through

91 -- was there anything about the review of the individual cases, particularly in the patients treated with sirukumab, about, again -- qualitatively, was there anything about the individual case review that might suggest a different pattern in the MACE events in terms of timing or type of event compared to what you would have expected based on your collective knowledge?

DR. MAYNARD: No, there was not.

DR. CURTIS: Okay.

DR. SOLOMON: Michael?

DR. WEISMAN: Obviously, these deaths and malignancies stand out, and that's what a lot of the focus of the discussion is here. Were you able to take a look at the baseline characteristics of those patients, with malignancy or early deaths in the trial, to get some idea of what the risk factors were? And were the patients that died that crossed over, were they enriched because they were really sick to begin with?

What is that telling us about who we give these drugs to? Because if you look at all the

meta-analyses that have been done for this, they show the same phenomena, and yet the observational cohort studies don't because maybe over time the patients that are sick get well with the drug, and that risk factor goes away. So everything kind of evens itself out.

So you see something early on, and it happens. And is that telling us about who we should be either testing the drugs in trials or using the drugs in the real world? What is that telling us when you look at the baseline characteristics of these patients?

DR. MAYNARD: This is Janet Maynard. We did do qualitative and quantitative analyses. We looked through all of the different narratives to see if there was something about those patients, and we also looked quantitatively to see if there were differences that would call out a specific patient group or type of patient that would be higher risk, and we were not able to identify any specific marker from our analyses of that, where we looked at the information that would identify

patients who would be more at high risk.

Just as a general comment, when we're not comparing directly with other biologic programs, I'll say, in general, the types of patients who are enrolled in these trials tend to be similar in terms of these are patients who have tried multiple therapies and may have comorbidities. But I don't think that's very different from clinical practice when you're considering who you might use an IL-6 inhibitor on.

DR. SOLOMON: David Felson.

DR. FELSON: David Felson. Rather than tell us the number of deaths per trial, can you give us rates per 100 person-years? Because that was a bigger trial with longer follow-up. It would be helpful, so that we don't get a sense that there's at tremendous imbalance there.

DR. MAYNARD: We do not have that information with us right now. The sponsor may have that information.

Do you guys want to show that?

DR. SOLOMON: So we're looking for the rates

of death across trials.

DR. SUAREZ-ALMAZOR: They are separate trials.

DR. YEILDING: Newman Yeilding, Janssen clinical development. Just to also point out exactly what Dr. Felson pointed out, one of the reasons that there are more deaths in the ARA 3002 trial is it's a much larger trial. It's about twice as big as ARA 3000 and -- I'm going to bring this slide up. You can see the relative mortality rates between the two trials first line, which shows the rates per 100 patient-years of follow-up, so 0.81 and 0.49. Slide back up. Thanks.

DR. SOLOMON: A couple of questions that I have for the FDA. Can we bring up slides 119, and then a similar question on 120? I just wanted us to go over these data a little bit more because now we have an active comparator within the program; we're not trying to compare across programs. And we're looking at obviously an approved drug versus the applicant's drug, and just to digest this information to see the SAE rates across the

50-milligram versus the adalimumab. Then, could you just bring up 120 as well?

I guess the question that I have for the FDA is just thinking about the laboratory abnormalities and the clinical adverse events, the sponsor's raised this question about biologic plausibility, and I'm just curious. I'm sure you've thought about biologic plausibility of the adverse events, and the mortality, and some of the lab issues. Maybe if you could expand upon that question.

DR. MAYNARD: If you could go back to slide 119. As was mentioned, this slide shows a comparison of adverse events of special interest comparing adalimumab to sirukumab 50 milligrams and sirukumab 100 milligrams. And as has been mentioned, in general, you see more events and a higher incidence rate for these adverse events of special interest on either of the sirukumab doses compared to adalimumab.

We do acknowledge that this is a fairly small trial and that there are a limited number of events, so a higher incidence rate could be driven

by just one or two event differences. But in general, there is a consistent trend for more of these adverse events of special interest on the sirukumab arms compared to the adalimumab arms.

In terms of biologic plausibility, we thought it was important to look at an easy biomarker being laboratory abnormalities, so if you'll go to slide 120. We did look to see if there were differences in the laboratory parameters, which potentially could help explain any of the differences in these adverse events of special interest. And in general, again, it's seen that there were more laboratory abnormalities related to both neutrophil and the liver function tests and lipids, which are shown on the next slide in the sirukumab groups compared to adalimumab.

We recognize there are some limitations given the small size, but I think you can see clear trends in these data.

DR. CHOWDHURY: You addressed the question about biological plausibility, and we did really think about it. And as Dr. Maynard mentioned, the

counts that are of relevance in neutrophils for the infection, lymphocytes, and these laboratory changes of lipid parameters, and with a comparative trial, we have a difference. It's very difficult really to pinpoint one is causing the other. And we often have looked back, and those that have serious infections or [indiscernible] infections and the neutrophil counts, they usually do not correlate 1 to 1, but in general, what you saw is what you saw.

One thing to also point out here is the nominal difference of the dose is about 4-fold. The exposure difference is about 6-fold. And across the doses of the sirukumab going down to 25, the laboratory changes were more or less similar across, which is somewhat remarkable because this is a very sensitive marker. The laboratory changes and looking across varieties of programs, it's not consistent, but generally you see a difference of laboratory parameters. Here we don't.

DR. SOLOMON: And it was mentioned, but it wasn't dwelled upon in the presentation, the

comparison with the other IL-6 drugs working on a similar mechanism. I know it's not the same mechanism, but a similar mechanism. And the mortality difference was not seen in those with those drugs. But the laboratory issues, was there similar kinetics observed with the laboratory?

DR. CHOWDHURY: Yes. Let me make some comment, and Dr. Maynard may have something to add here. For the mortality again, with the full limitation across study comparisons, it has a lot of problems. But for the other two IL-6 targeting drugs, compared to placebo, no differences of any remarkable magnitude for mortality was seen. Again, the number of events were small. That side was very, very different.

As far as the laboratory parameters goes, generally they were of similar nature in terms of the items were changed in the magnitude of changes. The difference was, for the others, there was somewhat of dose response between different doses tested, which was not the case for this program.

Janet, do you have some information?

DR. MAYNARD: I agree with what's been said in terms of comparisons across with other IL-6 inhibitors.

DR. SOLOMON: Just to follow up, the MACE issues that we observed and the lipid abnormalities, I don't know if anyone -- I mean, there's been a lot of controversy around lipid abnormalities with these drugs, and inflammation, et cetera. But I don't know if you've all thought about the LDL relationship with MACE and how these LDL changes might or might not correlate with the observed differences in MACE.

DR. MAYNARD: And just to clarify, when you say observed differences, do you mean observed differences between IL-6 inhibitors or within those?

DR. SOLOMON: Within.

DR. MAYNARD: Within the sirukumab program.

DR. SOLOMON: Exactly. Sorry.

DR. MAYNARD: Right. Of course, with the IL-6 inhibitors, we were interested in lipid abnormalities, and they were seen in the programs

with increases in LDL, HDL, total cholesterol, and triglycerides. So we were also similarly interested to see if that potentially translated into any differences in MACE.

As Dr. Borigini said during his presentation, there were imbalances in MACE noted. The imbalance, though, that was most striking was between placebo and the sirukumab 50-milligram dose group. And we don't really have a good explanation for why it might be different for one sirukumab dose versus the other, but that was of course of interest to us given the lipid abnormalities that were seen.

DR. SOLOMON: So another question that I have is you detailed very clearly the conversations between the sponsor and the FDA, and the design of the trials, and the escape options. Those were carefully thought out, and they allowed for feasible and ethical trials. And the efficacy analyses I'm sure were pre-planned and clearly laid out, but clearly we're now sitting with safety data that are difficult to interpret with the sponsor

giving us three different takes on the data.

I'm just curious what was the pre-planning that went into the safety analyses after the introduction of these complicated escape designs.

DR. CHOWDHURY: I'll take the question, and then I'm pretty sure someone else will also jump in here. This is a challenge. This is really a challenge. And the discussion that happens between the FDA and the industry at these early stages has been historically for the RA programs mostly surrounding around efficacy.

As for safety, we have a general expectation of approximately a thousand patients, give and take some, maybe a bit more, exposed over a year of the proposed dose. And then safety for this crossover, I think looking at this program and looking in the future, we have to think about that more. If we have to go back in time, I think one would question whether these crossover programs actually allow for a proper assessment of the safety, and it is really fraught with so many complications, one really has to think about it.

But historically, we have looked at those programs and have relied on them for approving the products. Here, the complexity has come up with this all-cause mortality having been imbalanced. So I'm answering question sort of tangentially, but that's the discussion that happened. It was not really prespecified, thought out, what safety would happen and how do you address crossovers.

DR. LEVIN: Greg Levin, FDA. I would agree. I think the amount of prespecification for safety analyses was minimal. It was mostly descriptive statistics. There were some conversations at like a pre-BLA stage about integrated safety analyses, and recommendations were conveyed. And some of those analyses were included in the application that tried to both integrate studies and include analyses that compared treatment arms and included post-escape data. But even those, in say like the ISS plan, had limited details on exactly what was going to be done, and so there's been a lot of back and forth about that during the review.

That's not uncommon. And I would agree with

Dr. Chowdhury that we're having additional discussions about both design and appropriate safety analyses, and extent of planning, and other similar criteria.

DR. SOLOMON: Thank you for being transparent and explicit about that. The tipping-point analysis was a sensitivity analysis that was performed for missing data with respect to efficacy. But as I was watching the presentation, I was thinking, so what about a tipping-point analysis for safety, and I guess were those performed, and how would they inform what we're looking at now? Because again, we're struggling with different analyses of incomplete data.

DR. LEVIN: This is Greg Levin, FDA, again. That's a good question. I think it's challenging to carry out those kind of sensitivity analyses even when we have a thousand patients, and convincing evidence, and an efficacy analysis. And here we're talking about 10 events.

So I would agree doing additional analyses that maybe have more or less assumptions about

comparability between patient groups and things like that have some utility. The applicant did some of those. Again, there are some limitations to those as well, and at the end of the day, we still see the imbalance that we're all wrestling with.

DR. SOLOMON: Well, if there are no more -- Dr. Meisel?

DR. MEISEL: Just one more question. One of the deaths that we talked about was a motor vehicle accident. Another one was a procedural complication of some type. First, can you tell us what that procedural complication was?

Then secondly, I know you're not supposed to do this, but if you remove those 2 deaths from the analysis, am I correct to assume that all of this discussion would stay the same, that the impact of those two is minimal in terms of this discussion here, that it's just not a big enough impact to worry about?

DR. MAYNARD: On table 34, page 64 of our briefing book, we do have the details of all the

different deaths in terms of when they occurred in relationship to the last dose of drug and what the death was as said by the investigator. So hopefully that has the information you're looking for in terms of the different causes of death across the program.

DR. MEISEL: Actually, I was looking at table 33 where it said something to do with --

DR. MAYNARD: That is a system organ class related to injury, poisoning, and procedural complications. I don't remember what the verbatim term is related to that. I don't know if the -- it may be, looking at this table, that that is the road traffic accident itself. And the sponsor can correct me if I'm wrong, that the road traffic accident that's listed in table 33 is under the system organ class of injury, poisoning, and procedural complications. Yes.

So the reason we put this table in here was just so that you get a sense of the breadth and scope of what people were dying with. So the things that are far left-justified are the system

organ class, and then slightly indented is by preferred term. So the preferred term is road traffic accident and the system organ class of injury, poisoning, and procedural complications. So sorry for that confusion.

DR. SOLOMON: Dr. Brittain gets the last question. You're between us and lunch.

DR. BRITTAIN: Gee. A very general question. Was a lot of discussion about that phase 2 dose-finding study -- at some level, are you wondering would the risk-benefit have been better with the 25? Is that what this is about?

DR. CHOWDHURY: I want to take the question. Really, it is a very complicated question that we would also like you to discuss. The phase 2 program here was approximately 30 patients per dosage, and all the doses were effective. Based on the data that we saw, we actually presented, choosing 100 q2 as the primary dose was not unreasonable. But the question is, how much really you'd rely on one small phase 2 study and then go on a large phase 3 program with the separation that

the phase 2 study showed between the 4-fold dose separation did not pan out.

So the question really is, is that something that is reasonable, or looking forward now with hindsight, doing another dose ranging somewhat larger, would it have pinned down the dose a bit better, safer? Unknown.

The question also came up of the dosing frequency. There was q2, q4, and q12. Understanding q12 was really meant as a very large separated dose, which would probably not show efficacy and would be safer. But again, q4 was also proposed somewhat in that direction, that with a 6-fold separation of exposure, the safety would separate out, and efficacy would separate out based on phase 2. But actually safety and efficacy did not separate out.

So it's a larger question of how much you rely on a smaller phase 2 study and do a large phase 3 program, and they do not really get the same thing that they were expecting.

DR. SOLOMON: Wonderful. That was great.

Thank you.

So now we're going to adjourn for lunch. We'll reconvene again in one hour, so not at 1, but at 1:10. So we have a nice leisurely hour. Please take any personal belongings you may want at this time. Committee members, please remember there should be no discussion of the meeting during lunch, or with the press, or any member of the audience. Thank you.

(Whereupon, at 12:09 p.m., a lunch recess was taken.)

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

(1:06 p.m.)

Open Public Hearing

DR. SOLOMON: We're going to get going now with the post-prandial part of the day. So we now have the open public hearing, and we have three speakers that have asked for time.

Both the Food and 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, 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 product, and 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, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such 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, and thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MARMARAS: Good afternoon. My name is Stephen Marmaras. I'm the director of state and national advocacy for the Global Healthy Living Foundation. I have no disclosures to make regarding my travel here today.

Good afternoon. Again, my name is Steve Marmaras. I'm the director of state and national advocacy for the Global Healthy Living Foundation. On behalf of GHLF, I want to thank this committee for allowing me to speak today. The Global Healthy Living Foundation is a 501(c)(3) patient advocacy organization that works to improve the quality of life for people living with chronic disease by making sure their voices are heard.

GHLF represents more than 100,000 chronically ill patients and their caregivers across the country. Many of these individuals are a part of our online arthritis community called

CreakyJoints. The have rheumatoid arthritis or other related autoimmune diseases and have had their lives changed because of biologic therapies.

The patients we serve utilize the internet to connect with other patients around the world to help them navigate an environment that can be scary and overwhelming. They are committed to staying informed with the latest research on autoimmune arthritis and creating dialogue with others fighting these diseases.

On behalf of this community, we are very pleased to be here to discuss a novel therapy approach as it represents expansion of the available tools that may enhance the quality of life for the patients in our community.

When we asked our community what they would like us to say to FDA and the Arthritis Advisory Committee today regarding the approval of a new biologic, we heard a similar message across the board. Whether it was Judy in Sandusky, Ohio, Lisa in Lake Stevens, Washington, or Rick in Indianapolis, Indiana, they all had shared

experiences learning to live with pain daily, but also having to cope with the frustration and anger of loss of physical independence.

They have tried many, many biologics, some that have worked, some that have worked for a short period of time, and some that have caused intolerable side effects. In fact, the majority of RA patients in our community try four or five biologics before achieving stability.

We feel that approval of this BLA is a much needed additional medical option for patients unable to find a suitable treatment. We also believe it positively impacts many issues that our patient community cares about. They are as follows:

Number one, patient-centric drug development. We are extremely encouraged to find that the sirukumab's mission deliberately seeks to address lifestyle challenges that accompany the disease. Our community appreciates that the sponsor has developed a version of the autoinjector vehicle specifically designed for patients with

severe dexterity limitations from their joint degradation. Theoretically, this will allow patients with even the most advanced forms of RA to maintain independence in their treatment compliance.

Many RA patients suffer from needle phobia and have difficulty self-administering their therapy. Some travel to a physician's office for assistance in administration. A 4-week dosing schedule as proposed is very convenient relative to other treatment options in the class for those with mobility and travel restrictions.

Number two, additional treatment options. Rheumatologists and their patients need more treatment options with diverse methods of action to target different aspects of the disease. Our community tells us that the path to finding a biologic that works for them as an individual is not an easy one. It is a physical and emotional roller coaster ride. There is a lot of trial and error involved and patience and persistence are key.

Again, Lisa from Washington tells us that her medical options are dwindling now that her sixth biologic recently ceased being effective. She expressed that this is demoralizing and feels as though the light at the end of the title is dimming.

Lastly, emphasis on PROs. As a contributing patient-powered research network to the National Patient-Centered Clinical Research Network, or PCORnet, we believe the sponsor should be applauded for their strategic choice to pursue patient-reported outcomes in phase 3 trials. This likely allowed them to assess attributes that patients consider to be most important, such as pain, fatigue, quality of life, and physical function. We hope that future FDA submissions emphasize PROs, as we believe they are making health research more efficient, and powerful, and less expensive.

CreakyJoints is honored to facilitate the use of PROs through our own arthritis-powered national patient-reported outcomes registry.

Ultimately, we always put our faith and trust in the experts at FDA to keep us safe and approve drugs such as this one, based on their safety and efficacy.

We respectfully offer our support for this submission due to its patient-centric approach and as a much needed additional treatment option. We thank the FDA for emphasizing the value of the patient perspective through public meetings such as this one, and will continue to mobilize our patient community to create a better life for those who will benefit from therapies like this one. Thank you for your time and attention.

DR. SOLOMON: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WESTRICH-ROBERTSON: Hello. My name is Tiffany Westrich-Robertson. I am representing the International Foundation for Autoimmune and Autoinflammatory Arthritis. I am also a rheumatoid arthritis patient myself. As far as disclosures,

Janssen did help fund my travel to get here, as I had expressed a dire concern for being able to stay [sic] here before you today.

First, I do want to thank the FDA and the advisory committee for your time. I was diagnosed with rheumatoid arthritis in 2009, two years after initial onset. Three years into my journey with RA, I started a biologic treatment. I immediately failed that biologic, a TNF inhibitor, and was switched to a biologic with a different mechanism of action.

After three years with my RA fairly well managed, that biologic also failed. The third biologic I have been on now for almost two years has done well, but my disease activity and quality of life is starting to diminish rapidly. And I'm not sure how much longer I'm going to be able to run the International Foundation for Autoimmune and Autoinflammatory Arthritis and represent patients if I can't get this under control.

Now that I have failed this third biologic, I worry about what is in store for me and patients

like me who are not responding well to existing mechanisms of action. I am in what should be the prime of my life, yet my ability to function both professionally and personally is getting progressively challenged.

While many patients do have success using existing treatments that are available, a significant percentage do not. This is especially important given the progressive nature of the disease and the potential for permanent and irreversible damage that can happen if the right treatment is not applied.

RA is not a one-size-fits-all disease, therefore what works for one patient may not work for another. Many patients either do not respond initially or they stop responding when a treatment loses efficacy over time. Therefore, alternative treatment options and mechanisms of action are needed to address the growing needs of patients who do not respond.

As you have heard from the panel, this particular biologic targets IL-6 cytokine, not the

receptor like the others on the market. This new mechanism of action could have significant impact on patients who are not responding to existing similar types of treatment. Many of these patients have been affected by RA for quite some time, which is why they have tried most, if not all, of the treatments currently available.

The patients that I was able to speak to prior to arriving today, many of them have tried three, four, five, six different biologic treatments, and they're feeling a sense of desperation. Some have exhausted or are near exhausting their treatment options. And the one continuous sentiment that was expressed over and over by that patient population was, "I'm scared. If I fail again, I have nothing."

I would like to acknowledge the attention to quality-of-life assessments, as most patients do report fatigue is their most bothersome symptom. As a matter of fact, many patients state they would choose a treatment based on fatigue management over a clinical response simply because the fatigue is

so debilitating and limiting in daily life.

For patients who have not responded to other treatment options, this is even more significant because the damage they have is permanent and irreversible. Fatigue as a potentially manageable symptom is of high interest to our community. Managing it could lead to more productivity and in turn less disability.

In a patient population where the disease is so varied per individual, access to new mechanisms of action are necessary so a greater percentage of patients can achieve clinical improvements and acceptable quality of life. The longer patients have to wait for the right mechanism of action that will work best for them, the more irreversible damage and unnecessary disability is possible. This will only lead to higher long-term complications and a larger financial burden to our healthcare system.

I am thankful to have had the opportunity to represent the voice of the patients who need more options in order to appropriately manage their

disease. I don't know what my next biologic will be, but I hope if the mechanism of action fails me yet again, that there will be new options available for me when and if I continue to digress. The clinical data clearly shows efficacious benefit and has a similar safety profile to other existing treatment options.

On behalf of the greater patient community, as well as in regards to my own personal journey, I thank you for your consideration to approve this new treatment option and in turn provide hope to those who are running out of options. Thank you.

DR. SOLOMON: Thank you, speaker number 2. Will speaker number 3 step to the podium and introduce yourself? Please state your name any organization you are representing for the record.

MS. MOSELY: Good afternoon. I am Stephanie Mosely, and I'm currently a patient of the Center for Rheumatology and Bone Research in Wheaton, Maryland. I'm actually here to give a small testimony of being an RA patient.

I walked into the Rheumatology Center nine

years ago with severe rheumatoid arthritis. I had 32 swollen joints at that time. My first year inside of the clinical trial, within that year, it changed drastically for me. I went from 32 swollen joints to 20, and still today I am able to function normally like I've been doing before that time.

Before those nine years, it gave me very much trouble. I had to actually end up interrupting my mother's life. She had to move out of her home to move with me because I could no longer function. I could barely walk. I couldn't raise my arms. It was so severe that I could barely talk.

So to this point, I'm just here to thank pharmaceutical companies for finding medications that work. Out of those nine years of being in the clinical trial, I have done three different pharmaceutical physicals, and all of them have been able to work for me. I've never had one side effect at all. I take the medications every day and every two weeks for the past nine years, and it's been very successful for me. So I thank you

again for having medications that work.

Clarifying Questions (continued)

DR. SOLOMON: I want to thank all the public speakers. I think we've exhausted the list, and the open public hearing portion of the meeting is now concluded, and we'll no longer take any comments from the audience.

We do have some time, and I think there may be some leftover questions from the morning that might be clarifying questions that could be posed to either the applicant or the FDA before we move on to the discussion.

Are there members of the committee that want to ask further questions? Dr. Katz?

DR. KATZ: James Katz from the NIH. I'd like to ask the FDA how they look at the outcome measures of effectiveness when they, the DAS and the ACR score, includes the CRP in some of those measures, and your view of that for the IL-6 pathway trials, what that implication is.

DR. LEVIN: This is Greg Levin, FDA. It's one of the reasons why we look at the components of

these multi-component endpoints carefully to see what the nature of the benefit is. And as was illustrated by our presentation, there was consistent evidence of effects on the various components, not just the inflammatory biomarkers, so HAQ, a patient-reported outcome measure, of physical function, patient global, physician global. So we saw evidence of benefit across the other dimensions of these multi-component endpoints.

DR. KATZ: If I could just follow up. But admittedly, it's a degraded effect when you look at the tender joint count or the swollen joint count, and it's less robust -- no -- if you look at that in isolation as an effectiveness measure compared to looking at the DAS that includes the CRP.

DR. LEVIN: The evidence was strong. If you're talking about the magnitude of the benefit, I'm not sure how to compare the magnitude of the benefit on, say, CRP versus swollen and tender joints. I think we could talk about -- we could put the -- let me see if I can find the slide.

Can we put slide 40 up? This is from study 3002. This is showing estimated effects on the far right for the two different doses of sirukumab versus placebo for the different components. And then slide 41 is in study 3003. So we have mean differences between treatment arms and 95 percent confidence intervals.

The magnitude of the effects, I think that's up for discussion if you want to talk about whether they're a magnitude that you think is meaningful or not. But just from an evidence of effectiveness perspective, we did see relatively consistent evidence across the components.

DR. SOLOMON: Ms. Aronson?

MS. ARONSON: Thanks. Just to follow up, earlier I had asked for a slide, the list of exclusions, and the sponsor thought that they would get that after a break.

DR. SOLOMON: Go ahead.

DR. VRATSANOS: Slide up, please. This will be a little bit hard to read. This lists all the major exclusions in a trial. Is there a particular

one that we can point out that you might be interested in seeing?

MS. ARONSON: No. I'm recognizing that it's extensive, but thank you for providing that.

DR. SOLOMON: Maria?

DR. SUAREZ-ALMAZOR: Yes. Suarez-Almazor. I just wanted to clarify an answer that the FDA gave this morning to the panel to make sure that I understood correctly. I think they asked, or someone asked, whether the other two IL-6 receptor inhibitors had the same signals, and I believe that was with respect to death or serious adverse events.

I believe that you said no, but I'm not sure if the question was asked with respect to some of the other adverse events, like for instance, the level of neutropenia or even the infection rates. And I understand that you don't want to do indirect comparisons, but I think that for us, it's important to evaluate this considering the other agents that have a similar mechanism of action.

DR. MAYNARD: So probably the easiest

question, or part of that question, to answer is about laboratory abnormalities, which there are limitations comparing across studies. But we did look to see if the magnitude of the laboratory abnormalities were somewhat similar across the different IL-6 inhibitors approved, and then also sirukumab. We did find that, in general, the laboratory abnormalities were within the range that we have seen with these drugs.

In terms of the more difficult question of comparing specific adverse events of special interest, Dr. Borigini did review some of the label information that's included currently and the prescribing information of the IL-6 receptor inhibitors, and as you are aware, there is a box warning regarding serious infection that may lead to hospitalization and death. So that is a safety signal that has been identified previously.

I think the main safety issue that we really were focusing on this morning was related to death. I don't know if Dr. Chowdhury.

DR. CHOWDHURY: Again, noting the

limitations, that is very difficult to compare across studies. For example, in some of the programs, when a placebo patient is removed because of swollen and tender joints, they're not necessarily randomized back to the active treatment; rather put on long-term extension. In some of the programs, they're put on one of the two doses. Here they're equally randomizing two doses.

So these are all complex to put comparisons across. But if you look at the product label of the two IL-6 targeting drugs, the mortality imbalance against the two drugs was not there. In fact, if you look at the individual labels to see the numbers, the mortality for the drug was approximately 0.4, 0.5 per hundred patient-years for the drug, but the placebo was approximately 0.8 or so, give and take, again, a very small number of deaths. It's not meant to compare across the programs. The high-level issue is, in the controlled portion of the two IL-6 targeting drugs, there was no mortality imbalance against the drug.

DR. SUAREZ-ALMAZOR: And I understand what

you say, but on the other hand -- I mean, the death rate for the drugs is very similar, and what's different is really the placebo rate of what was seen for the IL-6 receptor drugs versus what's seen here. I mean, that raises some concern because the population, there's no reason to think they are different. When we look at the baseline characteristics, they all had failed DMARDs and so forth.

DR. CHOWDHURY: Yes, this is very important, and this is the reason we are gathering here to discuss. It's very, very true that the general -- across these studies, you do see that and fully acknowledge Janssen showed the slide, and it is true. But I think the question really is how much reliance you can have across programs done over decades to make a conclusion based across.

So that's the reason we come back and look at the program, at a program, and compare against the placebo. And the problem here is it is complicated because of the crossover design of all the programs. But historically, for other

programs, we [indiscernible] to the programs -- programs of the imbalance, and accepted those to move forward to approve those drugs.

DR. SOLOMON: Ms. Aronson?

MS. ARONSON: Diane Aronson. Slide 64 was label information about approved antibodies to the IL-6 receptor. I'm just wondering have we seen a proposed label for the product that we're reviewing, number one. Number two, I don't notice malignancies on this list, so is that not something that would be highlighted?

DR. MAYNARD: Right. So we have not shown a proposed label for Janssen today in our discussions. I'm not sure if Janssen has something that has an overview of what they were considering would be in their proposed label.

Do you have a slide that you can show with that information?

DR. VRATSANOS: We felt it would be a bit premature if we showed a proposed label. What we can say is that based on the safety information Dr. Yeilding provided, we view that the risk of

malignancy, specifically, is in line with what would be expected in RA patients treated with biologics and that there's no excess risk with sirukumab. And we're proposing labeling generally similar to the other IL-6 members of the class.

DR. MAYNARD: And just one follow-up. You had asked about specifically malignancies and the currently approved labels. So the currently approved labels discuss immunosuppression and note that the impact of the treatment on the development of malignancies is not known, but that malignancies were observed in the clinical study. So that's somewhat of the wording in the current labels right now.

DR. SOLOMON: David Felson?

DR. FELSON: Dr. Felson. I guess I want to switch back a little bit. We're all struggling with how to interpret this safety data, and I'm not sure there's an easy way to cope with that struggle. So I wanted to pose it a little differently and wonder if this is acceptable to the FDA.

My sense from a distance is that we now have the benefit of many opportunities, second-line drugs and biologics in rheumatoid arthritis that the FDA has graciously approved, by my count, 16 biologics and 9 second-line drugs for rheumatoid arthritis, all of which have an efficacy profile not dissimilar from the one we're dealing with now.

One of the questions is, that I'm struggling with, recognizing that we're not able to definitively determine how safe this new agent, is whether the marginal efficacy provided by this is worth a safety signal that might be concerning. So that's the question I'm beginning to pose in my head.

So I want to, in that vein, go back to efficacy data -- not safety data -- where we have a little better information. Because, to me, that is the important, emerging question, that with a very large armamentarium of efficacious biologics and second-line drugs, and an armamentarium that frankly is going to get even larger regardless of what we do here, the question is, is it worth a

potential safety signal that may be different from other second-line drugs we have?

As I look at the data -- and I'm actually looking not so much -- well, I can pull up slide 42 of the FDA's presentation. As someone who was involved and led the development of ACR20 and 50, I don't think I would worry -- I know you looked at the primary outcome of ACR20, but I think what matters to patients more is an ACR50 or 70 response, having listened to the patients, and saying, okay, major responses to this therapy in patients who have failed other therapies, which I think is what the argument is here.

The argument being, okay, we need something else that might afford an opportunity for major improvement for patients given what's already available. Does this new therapy provide that new opportunity for improvement? And I look then at ACR50 and 70 compared to rates in placebo.

Let's look at, for example, ACR50 --

DR. SOLOMON: This is the DMARD inadequate response.

DR. FELSON: Yes, I know, and we're going to get to the TNF inhibitor one in a minute, which isn't nearly as promising.

Actually, this isn't compared to -- oh, yes it is. Placebo rates are there. So of 100 people treated with this new agent who have failed DMARDs, roughly 30 percent of them will have an ACR50 versus 12 percent on placebo. So that's an 18 percent or a little less than 1 in 5 likelihood that their improvement is going to be related to this new therapy. In ACR70, it is about a 1 in 10 likelihood, meaning that if they fail second-line drugs and they get this agent, their chance of getting major improvement is about 1 in 10.

Now, that is against the substantial safety concerns that we're grappling with here. So now, if it's used as is likely, to treat patients who have failed biologics -- witnessed all of the patients who gave us advice about this, and thoughtful advice I think. I don't know where that equivalent -- I think it's the next slide, maybe 43. There you go.

So now we're looking at ACR50 and 70 rates. So the chance of getting an ACR50 response from this new therapy is 10 percent, 1 in 10 people, compared to placebo against that safety signal. The chance of getting an ACR70 -- which I think everyone in the room would say thank goodness they got an ACR70, this is great, they're nearly in remission -- the chance of that occurring is, given the dose 50 milligrams versus placebo -- and let's average the 6 and 10 percent because these are very imprecise estimates. Let's call it 8 percent, about 5 percent difference versus placebo.

So 1 in 20 patients treated with this new agent would experience an ACR70 if they'd failed biologics or multiple biologics. So then the question is, is that efficacy equation worth these substantial safety concerns that we're discussing here and recognizing that those safety concerns are uncertain to some extent?

I guess, to me, that's the emerging question. It is not so much what is the safety concern. I think we're all, after having discussed

this for a while, not entirely sure what the safety concern is, and I don't think we can be sure. I think you've done a nice job of telling us that.

I think the question ultimately is, so is this worth that safety concern? This does not provide dramatic results or responses to people who have failed these other treatments. And looking at the document that you guys nicely provided on all of the other therapies that are now approved and more to come, is this an important new element of our armamentarium given that we have 16 biologics already, and 9 small molecules already, and more to come, or maybe given the safety signal, is this not such a good choice?

You don't have to respond.

(Laughter.)

DR. CHOWDHURY: Since I pressed the button, I'll probably try to share the talks, not respond. It's a very charged, loaded question, which is best discussed by you all.

I think the issue here is do we have any clear evidence that this particular product works

in some patients where some of the products have not worked. I mean, the data is not really there to certainly prove that, but one would probably say it may be.

The historical thing that we see of patients coming in of DMARD inadequate responders, or TNF inadequate responders, are the history. And if you want to really prove that, you probably will have to put back those patients into where they're not responding to make sure they're actually truly non-responders, which is a very tall order, and typically one would not do that.

So it is really another choice, but not necessarily you can pinpoint very clearly, for the purpose of practice or labeling, that this drug will give benefit in such aspects that other drugs would not. It's just not there in the program yet, that we could see, but again, it's your call.

The other aspect is, this whole design of the program with the 100 q2 was expected, meant, designed, whatever you call it, to beat an active comparator, and yet the results aren't there. And

it is not uncommon for other programs to benchmark against something. So the best data that you have is the study 005, and some of the programs have done similar or some are different active comparator studies.

It is not uncommon in the development program for one drug to beat another marketed drug on efficacy. Here, we have the information. It doesn't seem like it gives advantage over another existing drug, again, not to say every other drug in the market.

Janet, do you want to add anything?

(No response.)

DR. SOLOMON: I think we're starting to move towards discussion and not clarifying questions. Do we have any more clarifying questions before we get the charge? And then we can discuss more, but we should just know where we're are in this proceeding.

Are there clarifying questions?

DR. MEISEL: I hope this is clarifying and not discussion. Earlier I asked the applicant

about the very high placebo response in 02 and 03. I'd like to get the FDA's take on that particular question. As well -- and this may be a question that would be inappropriate to ask or answer, so just say so -- for the other IL-6 drugs that have already been approved, was there a similar placebo response with those that would be considered -- this doesn't stand out like it seems to me to stand out here.

DR. LEVIN: This is Greg Levin, FDA. Placebo response rates in the range of 30 percent for ACR20 is pretty typical for rheumatoid arthritis development programs. I can't speak to the phase 3 trials for tocilizumab and sarilumab off the top of my head, but in general, we've seen placebo response rates in this range across RA trials.

DR. SOLOMON: Okay. Seeing no more clarifying questions, Dr. Maynard, you're going to provide us with the charge to the committee?

Charge to the Committee - Janet Maynard

DR. MAYNARD: Good afternoon. As we prepare

for the committee discussion and voting this afternoon, I want to provide a reminder of the issues: the regulatory framework for FDA standards for approval and non-approval of a marketing application and the questions to be discussed and voted upon.

As mentioned earlier, studies 3002 and 3003 provided evidence of sirukumab's efficacy for signs and symptoms, physical function, and radiographic outcomes in rheumatoid arthritis. The two study doses, sirukumab 50 milligrams every 4 weeks and 100 milligrams every 2 weeks, showed similar efficacy. Janssen has only proposed approval of the 50 milligrams every-4-week dose. In an active comparator study, sirukumab was not superior to adalimumab.

Moving to safety consideration, in the sirukumab clinical program, there was an imbalance in all-cause death with sirukumab over placebo. The rate of all-cause death was similar with both doses of sirukumab. The major causes of death include cardiovascular events, malignancy, and

infections. Sirukumab was associated with imbalances in serious adverse events and GI perforation. Also, sirukumab was associated with laboratory abnormalities, including decreases in neutrophil and platelet counts and increases in lipid parameters and liver function tests.

The Code of Federal Regulations, or CFR, states that FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. Note that we are not discussing manufacturing and labeling today. While these may affect decisions regarding approval, the discussion today is limited to safety and efficacy.

The standards for efficacy are shown on this slide. The regulations specify the need for substantial evidence consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the

proposed labeling.

The safety standard addresses three scenarios which could underline our refusal to approve an application, including that it does not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use, that results show that the drug is unsafe for use, or that there is insufficient information about the drug to determine whether the product is safe. Please keep this framework in mind as you consider the questions for deliberation today.

The first question for the committee is a discussion question. Specifically, discuss the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying antirheumatic drugs or DMARDs.

Question number 2 is a voting question related to efficacy. Overall, do the data provide substantial evidence of the efficacy of sirukumab for the treatment of adult patients with moderately

to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs? If not, what data are needed?

Question number 3 is a discussion question. Discuss the design of the 52-week placebo-controlled radiographic study ARA 3002.

Question number 4 is a discussion question related to safety. Specifically the question is, discuss the safety findings in the phase 3 program with particular consideration of the imbalance in all-cause death between sirukumab and placebo.

Question number 5 is a discussion question. Specifically, discuss the dose selection for the phase 3 program.

Question number 6 is a voting question related to safety. Is the safety profile of sirukumab adequate to support approval of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs? If not, what data are needed?

Lastly, question 7 is a voting question on

the committee's recommendation regarding approval of sirukumab 50 milligrams subcutaneously every 4 weeks for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs? If not, what data are needed?

Since this is a risk-benefit question, you may wish to consider your previous voting for the efficacy question number 2 as well as the safety question number 6 to be consistent. In other words, to vote yes to this question, you probably should have voted yes to questions number 2 and number 6.

I will now turn the meeting back to Dr. Solomon. Thank you.

Questions to the Committee and Discussion

DR. SOLOMON: Thank you. We have a complicated set of questions, some of them discussion, some of them voting, but I think there's a method to the madness.

So we'll now proceed with the questions to

the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel, and we'll talk about voting when we get to voting, but we can open it up now.

Again, the first question for discussion is the efficacy of sirukumab for the treatment adult patients with moderately to severely active RA who have had an inadequate response or are intolerant to one or more DMARDs.

Does anyone want to start?

DR. BRITTAIN: This is the easy one. Yes, the efficacy results are very robust, consistent across endpoints and sensitivity analyses.

DR. SOLOMON: Michael?

DR. WEISMAN: A lot of what we're talking about is based upon some of the previous discussion that we just had, and the points I think that David raised, and the points that Dr. Chowdhury answered. Over time, the inadequate response group of rheumatoid arthritis patients is getting tougher

and tougher and more difficult to manage. The old definition of an inadequate response was always what else is available? So patients have done well. So an inadequate response to biologic drugs is a tough group.

So is it fair to look at that change in score numbers that David just pointed out to us, mean-change scores in hundreds of patients of 10 to 12 percent -- the change score response in the more meaningful responses, is that enough?

Well, from a clinical standpoint, it is yes. And I think at this point in time, given the toughness of that group and the group of patients that we see, I think from a standpoint of efficacy, I think the sponsor has proven their case going forward.

DR. SOLOMON: Dr. Oliver?

DR. OLIVER: Alyce Oliver. I'm just actually concurring with Erica, and Michael and I said it pretty well. I think the data shows efficacy and is very consistent with the data from the TNF inhibitors, both methotrexate IRs and

biologic IRs.

DR. SOLOMON: Jennifer Horonjeff?

DR. HORONJEFF: This is Jen Horonjeff. I know that we're not talking about safety, so I will save my comments there. But to discuss what I'm reading here, we're talking about intolerant to one or more disease-modifying antirheumatic drugs. So when I'm reading that, per the discussion earlier about -- again, I won't go into safety, but given that safety profile that perhaps is questionable, is this really what we want to be thinking about? Is this going to be somebody's second line of treatment if we're questioning those things?

So I just bring that up. The efficacy, I agree. I do think that was delivered very well and it was comprehensive. But specifically, because that's what we're asked to be discussing, that's what's going through my mind, is at what point do we feel this is the appropriate pathway for people to then continue their treatment plan?

DR. SOLOMON: A point that I'd just like to make is I think, again, across the standard ACR20,

50, 70, typical efficacy, their x-ray progression, I think the case was made well and it's clear.

There was some discussion of the unmet need, which is a slightly different issue, but the needs around patient-oriented, patient-reported outcomes, mental health, depression, comorbidities. And while there was some positive outcomes with respect to the mental component score on the SF-36, I wasn't quite sure if those were clinically important changes or improvements. All the trends went in the right direction.

Again, those would be considered secondary outcomes, but I just think that that's part of the consideration as we think about the next drug, another drug. After having X number of biologics on the market, what's the incremental enhancement for patients having another one?

DR. HORONJEFF: I'll just quickly comment. Jen Horonjeff. I think in relation to that, as we have more and more treatment options and people are historically doing better than perhaps they were on prior treatment plans, that there can be these

ceiling effects with some of these other outcome measures. Even something like the HAQ, it's questionable whether we're actually capturing their full level of function with that.

So I do think that it's just an appropriate question to bring up, are these really what we should be measuring a certain quality of life for other PROs against.

DR. SOLOMON: Dr. Becker?

DR. BECKER: I was just going to comment on your incremental improvement statement because that I think is one of the things I struggle with, is the incremental improvement versus giving that N of 1 possibility for that personalized treatment. If that was the one patient that it was responsive with, then it matters, right?

So I think when you're looking at the nth biologic for the similar targeting mechanism and weighing the pros and cons of safety and efficacy, and then you hear that people are going through six, seven different biologics, and maybe this is going to be the one that finally puts them into

remission, or puts them into remission for a long period of time, it's hard. It's hard to cut that off before the opportunity is given.

DR. SOLOMON: Diane Aronson?

MS. ARONSON: Can someone help me with -- the not superior to adalimumab, was that efficacy -- what was that? I just need review on that.

DR. SOLOMON: Is it a clarifying question about whether --

MS. ARONSON: Both.

DR. SOLOMON: -- whether --

MS. ARONSON: It was found not to be superior.

DR. SOLOMON: Superior. So I think the -- and the FDA might want to jump in here. But my interpretation is that when we look at the efficacy data in the 05 study, that there was really no statistically significant difference in the efficacy data comparing sirukumab versus adalimumab. So it can't be considered superior to an existing approved therapy. It was a superiority

trial, not a non-inferiority trial, so it did not prove to be superior.

I'll just go one step further. There is another IL-6 inhibitor that has done a similar trial. I know that's not maybe germane here, but there has been a superiority trial if I'm remembering correctly.

DR. MAYNARD: I believe there is published literature comparing another IL-6, but we're just --

DR. SOLOMON: Yes. No, that's fine.

DR. FELSON: Since this came up, I actually do have a clarification question, and I think probably the sponsor has the answer to it. There was a comment just made about finally this would be one that put them in remission. We haven't actually talked about remission here at all as an efficacy endpoint. I'm wondering if the sponsor has any data on the proportion of patients in these trials that actually went into remission on these therapies or placebo and whether we might see that data.

DR. SOLOMON: Please?

DR. VRATSANOS: We do have the data. We can show you the data momentarily. In the study 3002, it was approximately 5 to 10 percent of patients achieving remission -- slide up, please -- using the very stringent ACR/EULAR, the recent definition, with, really, a minimal placebo response. So this is going out to 52 weeks with small differences between the doses that are really difficult to interpret. But both doses did increase the rate of remission. It's a very difficult endpoint to achieve in trials.

DR. FELSON: And that's for the 3002?

DR. VRATSANOS: Yes.

DR. FELSON: So what about 3003, the one that was TNF for biological failure? Were there any patients that reached remission in that?

DR. VRATSANOS: There were. We're trying to identify the data. So we're looking for the ACR/EULAR remission in study 3003 at 6 months. If we can't find it now, we can try to find that for you later.

DR. SOLOMON: Let us know.

DR. VRATSANOS: Okay. Sure. Erica Brittain?

DR. BRITTAIN: Going back to the active control trial 3005 and the discussion we were having a minute ago, when I'm looking at the FDA slide 54, if I'm reading it right, there did seem to be some results where the p-value's less than .05 I guess in terms from baseline for the DAS28, slide 54.

I assume the reason you're calling it not significant is it had to do with gatekeeping, which was considered primary and secondary. It looked like on the previous slide, the primary was the 100-dose. I'm just trying to understand why you were calling it non-significant.

DR. LEVIN: This is Greg Levin, FDA. You're correct that they had -- so they had co-primary endpoints, which were ACR50 and DAS28, and they did not show evidence of superiority on both of them. But perhaps more importantly, we looked at the components of DAS28, which is showing the

difference on this slide. And if you can go to slide 55 to see what was driving the difference in DAS28 that was observed, it was ESR.

So when you looked at the -- and this is similar to the question from Dr. Katz earlier about differences, although this is not versus placebo, this is versus adalimumab. The differences in DAS 28 were due to the expected greater effects on ESR, the biomarker inflammatory component, which is expected due to the mechanism of action. But for endpoints like tender joint counts and joint count patient global, you saw similar degrees of change from baseline on the different arms.

DR. BRITTAIN: And there wasn't a difference on the ACR50.

DR. LEVIN: Correct. So there wasn't a difference on ACR50. And then when you looked at the components of ACR, you saw differences in CRP but because of the nature of ACR, it can't be driven by one component because you have to have a certain magnitude of improvement in at least 3 of the 5, plus swollen and tender joints, whereas

DAS28 is a weighted combination, and it can be driven by one component.

DR. SOLOMON: Any other discussion points regarding efficacy?

(No response.)

DR. SOLOMON: Okay. So if we could put the voting question? The voting question, question 2, overall do the data provide substantial evidence of the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs, and if not, what data are needed?

We'll be using an electronic voting system for this meeting. Once we begin the votes, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen, and the DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

So I've just read the question, and we have flashing buttons before us. I think we can go ahead and vote. Again, if the data are adequate, it would be a yes; if not, then it's a no.

(Voting.)

DR. SOLOMON: Okay. Are we going to read the vote?

DR. BAUTISTA: The vote is now complete, 13 yeses, zero nos, zero abstentions.

DR. SOLOMON: We can go around the room with the voting members. Maybe we'll start at my right. Dr. Felson, you state your name, what you voted, and if you want to expound on why you voted that

way, you can.

DR. FELSON: David Felson. I voted yes because I thought the sponsor had demonstrated efficacy.

DR. BRITTAIN: Erica Brittain. I voted yes. I think the results were robust across all the important endpoints.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted yes. I think the data is very similar to what we see with other biologics.

DR. WEISMAN: Michael Weisman. I think the sponsor has met their burden, and I voted yes.

MS. ARONSON: Diane Aronson. I voted yes.

DR. HORONJEFF: Jennifer Horonjeff. I agree that the sponsor showed the efficacy. And again, I would like to applaud them on showing more patient-reported outcomes in their presentation. My vote was yes.

DR. KATZ: James Katz, and I voted yes.

DR. BECKER: Mara Becker. My vote is yes.

DR. SOLOMON: Daniel Solomon. My vote is yes.

DR. WALDMAN: Scott Waldman. My vote is yes.

DR. JONAS: Beth Jonas. My vote is yes.

DR. OLIVER: Alyce Oliver. My vote is yes.

DR. MEISEL: Steve Meisel. I voted yes. I would like to see some additional data, though, at some point, and that is comparing the efficacy of this to the other IL-6 agents.

DR. SOLOMON: Thank you for the comments that were made. We're now going to move on to discussion question number 3. Again, this is for discussion, discuss the design of the 52-week placebo-controlled radiographic study ARA 3002.

I think the FDA wants to get their money's worth from all of us while we're here, so they figured, well, we'll just ask them some questions to talk. But there's obviously a lot of interesting points that could be raised regarding radiographic progression in rheumatoid arthritis studies, plain x-ray, at what time points, and how do you deal with patients who escape.

I think this is a real issue. Obviously

going forward, is this still an important outcome? It's part of the guidance, and companies obviously spend a lot of time thinking about how to go along and comply with the guidance. So I think any input that we can give to the FDA and the broader community would be useful.

Perhaps I'll ask a question that's embedded here. Our x-ray finding is important in this biologic era. I don't know if anyone wants to expound.

(Pause.)

DR. SOLOMON: Sorry. I'm being reined in.

(Laughter.)

DR. SOLOMON: We have to limit our discussion to sirukumab, so let's talk about the sirukumab, the ARA 3002.

(Laughter.)

DR. SOLOMON: Was the x-ray data on sirukumab useful in our discussion, and could the design of 3002 or future sirukumab studies, you know -- Jennifer Horonjeff.

DR. HORONJEFF. Jen Horonjeff. Well, I'm

going to forget that I heard what you were previously proposing, but then perhaps answer part of that. What we're finding in our research when we're talking to patients is they do care. They do care about making sure that they're -- when we think patient-centered outcomes, people often think that's just patient-reported outcomes, and that's not the case. There are things that patients still care about that they might not be filling out on a form.

That is something that they do care about, so I do think that that's important for us to talk about and for people to think about as other studies go forward.

DR. SOLOMON: And the design, so here we had to, again, focus on what was before us. The issue with the imputation, last observation carried forward versus straight-line imputation, that was part of the analytic issues that the sponsor and the agency had to deal with in thinking about how to look at the radiographic data. Erica Brittain?

DR. BRITTAIN: So yes. I thought the

sensitivity analyses that the FDA did were very helpful. I like the fact that when they did the intent to treat, which would be the hardest to show efficacy, they showed efficacy, and I found that very convincing.

So if I understood it correctly, they were including -- the placebo patients who went on drug were counted as placebo patients like you would do a normal intent to treat. And the fact that that would still be significant, that's convincing analysis. You might not always be able to get that, though, because it will dilute the treatment effect.

DR. SOLOMON: Before we go on with questions, could we clarify that. So there are two different methodologies used. I believe one was a linear extrapolation. One was some form of imputation. And maybe you could just explain.

DR. LEVIN: Dr. Brittain characterized it correctly. The supportive analysis using alternative data included data in patients on placebo who escaped to sirukumab and attributed to

the arm they were randomized to. So it was an intent-to-treat analysis, so it was counted on the placebo arm. That was what the support of -- there was additional support of analyses with data not shown that were conducted, but that was the one that we showed. So she characterized that correctly.

DR. SOLOMON: Dr. Becker and then Dr. Weisman.

DR. BECKER: I may have interpreted this totally off, but I thought one of the questions, when I was reading through some of the prior material, was mostly the ethics of having someone on placebo for a year, and then the damage that they incurred over that year.

To me, although I find this information to be very helpful to show that even though clinically well-appearing patients who may be meeting that 20 percent improvement of ACR -- so they don't have to opt out or escape out early or late -- they're still accruing damage. But would I ethically want to keep a 52-week study on placebo? I probably

wouldn't, knowing that damage is incurring, and they weren't sick enough to require escalation of therapy at least per the design of the study.

Does that make sense? At least that's how I interpreted that question.

DR. SOLOMON: Yes.

DR. BECKER: And I think that that's a really important point we can probably weigh in on for future studies here because I think in this day and age, that's not acceptable, not anymore. But as a clinician, maybe I'm missing some patients who are incurring damage because I think they're clinically well or they appear clinically well. And that's a dilemma in the real world for sure.

DR. SOLOMON: So I think Dr. Becker's point is well taken, to broaden the discussion about this escape issue and the feasibility of conducting placebo controlled versus being able to escape towards active drug, and at what point and how that does potentially muddy the water, not just on radiographic outcomes but safety and efficacy, I think is part of what we're talking about.

DR. BECKER: Can I say one point, though, before you pass me on to somebody else?

DR. SOLOMON: Yes.

DR. BECKER: I did think that the sponsor did allow for an early escape and a treatment modification and a late escape. So I didn't think that they put anyone in harm's way, but I think it's a good discussion to ask the patients that met at least 20 percent improvement via ACR, is that good enough to allow them to stay on placebo for 52 weeks? And I would argue by this data that it's not. Right? Because that's still incurring damage. It's not good enough.

DR. SOLOMON: Dr. Weisman

DR. WEISMAN: There have been three things that have happened over time that are important to consider here, and I've been there over that time. The first is the evolution of the method. So now we have a method of looking at a two dimensional representation of a three dimensional structure and coming up with some accurate data. We can do that.

The second is the assay system itself. So

we pick patients who are going to rapidly progress so we have something to compare it to, so that's evolved over time. So now within three months, we can pretty much tell the difference between arm A and arm B when the assay system is picked. But the third thing that's evolved over time is if there's a difference in two Sharp score points, what does that matter clinically?

So those are the issues that we have to face and that we should discuss. But the fact is the sponsor did what they were supposed to do in an ethically appropriate manner. And the proper sensitivity analyses were done as our colleagues mentioned, and he responded. So I think they met their burden. Yes, they did show it, but remember those three things that have evolved over time that got us to this point.

DR. SOLOMON: Erica Brittain, and then David.

DR. BRITTAIN: I just have a quick question, and maybe it was already answered. But is there a reason why this endpoint, the radiographic

endpoint, couldn't be done earlier? Would it be meaningful at a half-year? And I have no idea. I'm asking that as a question.

DR. SOLOMON: David, you want to --

DR. FELSON: Let me try that because I've been sitting here struggling over -- this is a very difficult set of problems. I think many of the rheumatologists -- I'm speaking only for myself -- have trouble with the ethics of keeping patients on placebo for a whole year even if they're experiencing ACR20. I think there's been enough data now that these people are going to have radiographic progression and that that is concerning.

I think this study was a thoughtful way of trying to get around the problem, but I don't think it's likely to be the future way of getting around the problem. I think the future way is going to only allow people on placebo for a limited period of time.

Then the question is how do you determine what the structural change is? And I think some of

what Mike said is absolutely right. I think the other question is whether MRI or other imaging techniques that are more sensitive to detecting change over shorter periods of time might now become more likely to be the standard where you can see what's happening over a briefer period of time before you have to take people off placebo because I think we're going to have to take people off placebo.

So I think the sponsor did everything right at the time, but I'm not sure this design will survive for very long. I think we're all a little concern about damage occurring in this time frame.

DR. SOLOMON: Erica, did you feel like you got your question answered? Is six months an adequate time? You might see some small differences. I think that the other point that David spoke to was what's the threshold for escape? Because if you do look at x-ray changes, even at a ACR20 response, you still have some changes.

DR. BRITTAIN: What I'm also curious about is how much relationship there is between this

radiographic endpoint and the primary endpoints that they measure. Do you really gain anything more from this? And I don't know how correlated they are.

DR. SOLOMON: David, you want to --

DR. FELSON: There have been a lot of studies of that, Erica, and the answer is they're correlated, but not very well.

DR. BRITTAIN: Oh, okay.

DR. FELSON: And the TNF inhibitor studies, a lot of Jeff Smolen's publications have shown that what Mara suggested was often the case, which is people on second-line drugs and/or on placebo, followed over a year with no clinical difference or even improvement, showed radiographic progression that was not experienced by people on biologics who had the same clinical course. And that I think is motivating a lot of what we're seeing, that it's quite clear that biologics slow down the rate of radiographic progression.

DR. SOLOMON: But the modality is still unclear. What's the right modality? Ultrasound

has been part of that discussion, MRI. Is there a biomarker of radiographic progression that might be something we can measure.

Anybody else want to take this on? Michael?

DR. WEISMAN: But the MRI data is poorly correlated with the clinical response over time because at the end of the year, you'll still find synovial thickening and ugly-looking stuff on the MRI, that patient feels perfectly well, and there's been no radiographic progression.

So as we get more sensitive in the assay, the questions about what it means become broader and bigger. We don't the answer yet. Let's get it, but we don't have it yet.

DR. SOLOMON: Yes. DR. WALDMAN: Scott Waldman.

DR. WALDMAN: Thanks. Scott Waldman, Philadelphia. So I'm not a rheumatologist, but I'm a clinical pharmacologist. But my question has to do with the designs of these trials.

Is there a reason why, given the evolution of the disease and the available agents to treat

now, that trials can't now evolve into active -- instead of any element of placebo, now an active agent control arm, and then look for non-inferiority for any of the elements of the output at the end. Is there a reason not to do that? I'm just curious because that would fix all of this, including the trial that we're talking about today. Just asking.

DR. SOLOMON: I don't know if the agency wants to take that on. It's an interesting discussion point.

DR. LEVIN: This is Greg Levin, FDA. It's a very good question. I will say that we are -- the statistical group that covers rheumatology is having internal discussions about the feasibility of non-inferiority trials for establishing effectiveness for primary signs and symptom endpoints, as well as for important secondary endpoints such as radiographic progression. But we also would very much like to hear feedback from the committee on the utility of that kind of a study to evaluate sirukumab.

DR. WALDMAN: So just to expand on that, not only would it answer the questions that we're talking about right now, but it would also give an answer to the safety issues that we're going to be talking about in a few minutes. It would bring some clarity to those safety issues as well, with an active comparator arm instead of a placebo arm, it seems to me.

DR. SOLOMON: I'm getting reined in again. Sorry. You guys asked for broad discussion, and we're having this broad discussion, and then people keep nodding their heads.

DR. CHOWDHURY: You've been reined in. I'm Dr. Chowdhury here. Just to reflect back on the comment that you raised, I think this is a right time to discuss this trial sirukumab because at some point, we come to a crossroad whether we are there or not. I think what we wanted the committee to discuss was the conduct of this trial, which was done at the time point when some discussions was going on regarding how long a patient could stay on true placebo.

I think we heard from the committee that this particular trial, if it was done right, was done with properly checks and balances in place, but we also heard going forward it may be a challenge.

That brings up the broader question, which you're not getting into, but I think the safety aspect, which is also the next point of the discussions, and also the future x-rays, non-inferiority modalities is a very valid point for us to hear, and I think we already heard that. Thanks.

DR. SOLOMON: So have we finished the discussion or does anyone want to continue? But we have to focus on this trial.

DR. BRITTAIN: [Inaudible - off mic].

DR. SOLOMON: No. I don't think we want to go there. Yes. Sorry. And we don't have to vote. Thank you.

(Laughter.)

DR. SOLOMON: So we're going to move on now to question 4, again, another discussion question.

And this will definitely focus on sirukumab. Discuss the safety findings in the phase 3 program with particular consideration of the imbalance in all-cause death between sirukumab and placebo.

DR. HORONJEFF: Jen Horonjeff. Rein me in if you have to. So this, of course as a patient and representing consumers, is something that I care very deeply about. And I will share a story that this hearing today comes at an interesting time for me because on Sunday I actually attended the memorial of somebody with inflammatory arthritis who passed away due to serious infection.

At the same time, knowing that this person participated in clinical trials, although I had nothing to do with that, and I'm not going to get into her history, I find myself very conflicted about this. And then taking this away from this control trial and how therapies are prescribed in the real world, and going back to the exclusion criteria as well as the label -- and after you brought it up, I'm sitting there and I'm staring at this label, and I believe there were 8 precautions

and warnings. I don't know how they will necessarily appear on a label, but I don't think that we could even say that a fraction of the general population would know what these eight are, maybe one of them, serious infection perhaps.

So that's where from a safety standpoint I really question whether or not a consumer would be able to weigh out whether or not this is something that they should be doing. And then a very brief appointment, where we would hope that that conversation is happening, it's not. And as a patient myself, I get these drugs. I don't read the labels. I do kind of what I'm told, and I'm a very educated patient.

So I think weighing all these different things in, I bring that up as the patient's perspective on this. And I certainly appreciate what my patient colleagues in the audience had said about being excited that they measured PROs and all that, as I am as well, but just measuring and showing efficacy of improved quality-of-life measures should not outweigh the safety concerns.

So I still think that that is a very valid conversation to have around all of this.

So that's just my standpoint as a patient, is I still am concerned about this. I wish we had data to compare whether or not it was more effective outside of just adalimumab, but I'm still concerned in thinking about how this gets prescribed going forward.

DR. SOLOMON: I'm going to take the chair's prerogative for a minute before we keep going. I just wanted to have Philip bring up the points that Janet talked about, the safety standard. I think the safety standard is worthwhile for each of us to review because I think we have a difficult case. And I'm going to let people just read it for the next 30 seconds, and then we'll continue on.

(Pause.)

DR. SOLOMON: Okay. Maybe we'll keep going. Dr. Brittain?

DR. BRITTAIN: I guess I'm really on the fence at this point about the mortality results. I think it's possible the differences we're seeing

are because of the bias that the sponsor suggested. I think it's possible. The numbers are also relatively small; at least the placebo group is relatively small. So I'm sure the confidence intervals are big. At the same time, we don't know that it isn't real, and I don't know any way, given the data that we've seen today, that we can really come down on one side or the other. So I remain uncertain.

DR. SOLOMON: Dr. Meisel?

DR. MEISEL: I've been around way too many years, and I've seen lots of wonder drugs come and go. What we don't know here today is whether or not this is a statistical artifact or real signal. We just don't know, and there's no way by the end of today we're going to know.

So we are in a position of either approving a drug and then doing phase 4 trials, and then in a year or two either have a sigh of relief because it really didn't have the problem, it was artifact, or we pull it from the market and all the good people who have been taken this drug and rallying upon it

are up in arms because now we're taking away their effective therapy. And either way you do that, it's bad and it's wrong.

I think where I'm biased with this is that we've got two other drugs that are IL inhibitors, granted a slightly different mechanism, but the signals didn't appear there. And we have no suggestion of efficacy differences between this drug and those other two. If I was running a formulary committee, which I know this is not, this would be a no-brainer; you wouldn't add it.

Now whether we would say that the benefits outweigh the risks here, I think when we have a signal here that didn't exist with the other drugs, I think, yeah, maybe statistics. And going back to the value that David was talking about earlier, I have serious concerns.

DR. WALDMAN: I'm going to reinforce what's been said. It seems to me that 02 and 03, the trials created residual uncertainty reflecting the idiosyncrasies of the design of the trial and the potential for bias from the shifting of the placebo

groups. And that residual uncertainty didn't get dispelled by trial 05; it actually was supported by trial 05.

So we're left with number 4 there. There is insufficient information. We don't have enough information to know, as Steve was saying, whether this is real or if it's Memorex, for those of you who are old enough to remember that --

(Laughter.)

DR. SOLOMON: -- I'm dating myself -- whether the signal is a real safety signal or whether it's just an artifact of the way that the trials were designed. So we're sort of stuck in this place. And at the end of the day, it's the risk-benefit ratio. And I agree with you, the benefit, which is like all the other drugs that are in that class, do not outweigh the risks that might be there.

DR. SOLOMON: Beth Jonas?

DR. JONAS: I'm going to reiterate that. And I think the uncertainty about the 02 and the 03 are really the big concern. And I understand how

the data was analyzed and why there is that uncertainty. But when we look at the 05 study, although a number of people have said that the N is small, so some of this could be chance, if you really look at the numbers, if it were chance, it would go both ways.

So in all cases, on all the adverse outcomes, the sirukumab didn't do as well as the adalimumab. So if you're going to say that it's related to the sample size, then it should go both ways. And I think that's the piece of data that really makes me feel like the safety is not there, and that's more of what I'm relying on when I think about this.

DR. SOLOMON: Thank you. David, did you -- no. Diane, or Michael?

DR. WEISMAN: This is really a dilemma, isn't it, thinking about what we don't know about the safety. So step back a little bit and realize that there are more off-target effects with IL-6 inhibition than TNF. We know that. But is the ability of the practicing rheumatologist today,

with the proper monitoring of patients that have not responded, or failed to respond, or otherwise can't take or won't take a TNF agent -- is the ability to safely monitor them appropriate to allow this drug to go forward? This is what I'm thinking in my own mind.

My background, when I got out of the Navy in the 1970s, and I started treating patients for the first time, there were two drugs approved for rheumatoid arthritis at that time. One was Cytoxan and the other was gold. And within five years, I killed two patients, one on Cytoxan and one on gold, and that's never left me.

So I think about safety of drugs today, and I think about the ability to monitor patients carefully, especially when we know that they're at risk, and the comorbid conditions that they have, such as the ones that were associated with the deaths we heard -- cardiovascular disease, malignancy -- our ability to monitor for that, assess risk properly, and use a drug in a patient that is not able to take an anti-TNF agent or

another biologic, do I feel comfortable enough myself to prescribe the drug that I saw today with the data in that patient population, with my skills and my background? I would say yes, and that's the difference between somebody who doesn't take care of patients. I think I feel comfortable to do that.

But is that enough, me feeling comfortable, an experienced rheumatologist, enough to have the FDA approve this drug to be advertised to every Tom, Dick, and Harry that sees patients in the community? I'm sorry about that, but that's the dilemma that I see. So I'm okay with it, but is it okay for everybody else? That's the struggle I see.

DR. SOLOMON: Diane Aronson. Just commenting on the safety in relationship to the study design, I brought up the demographics with race that still is troubling to me because as I reflect on the demographics, the United States, it's not reflected in the study, and also the incidence of lack of robust response in the African

American community. So if this rolled out, would we see different efficacy or more signals on safety? I don't know.

The other thing is about the exclusions. The patients overall were I supposed more healthy or potentially more healthy starting. So I'm trying to figure out that and the recognition of the rate of death and serious adverse events.

DR. SOLOMON: Thank you. Maria?

DR. SUAREZ-ALMAZOR: Yes. I just wanted to mention -- going back to what was mentioned originally by David and was also discussed, we cannot really make these decisions without considering everything together in the risk-benefit ratio, and we have been asked to evaluate efficacy on one side and safety on the other side.

So to me, part of what I'm struggling with is the benefit of the drug given that this is a drug that's in the same class, mechanism, to other approved drugs. If this was a new agent that was targeting a different cytokine that hasn't been targeted before, I would probably be a little bit

more enthusiastic because I could see that it could fail a niche of patients that have failed everything else, but here I'm not sure.

I mean, there are already two drugs or two agents that are the IL-6 inhibitors, that there's no reason to think that this new drug is going to act in a tremendous different way to some degree. So to me, that's what is playing in my decision, and you can't really separate the efficacy and the safety without looking at what's available out there.

Again, I am not convinced that there is a particular niche for an IL-6 inhibitor. I haven't seen data to convince me about that because the toxicity profile is also very similar among the agents.

DR. SOLOMON: Sean?

DR. CURTIS: Hi. Sean Curtis. Again, this is obviously a very difficult discussion, but I think we have to remind ourselves that we have to consider the data at hand, the trial data, for the purposes of these regulatory considerations and

statutory standards. I don't think it's completely fair to talk about comparisons for which we don't have data.

So again, I would just caution us to be very careful about making clinical decisions based on experience, things that are outside of the actual data set that's available to us.

DR. SOLOMON: Any other discussion points, any other new points that people want to raise? Dr. Oliver?

DR. OLIVER: I guess this is more of a clarifying question. What would be the best way to not better represent the data but to have new data? So we've discussed that we can't keep people on placebo for extended periods of time, and the crossover is really muddying the waters in terms of the safety profile. So what would we do differently next time to try to clarify this? The non-inferiority is what you were talking about.

DR. WALDMAN: Yes, to an IL-6 inhibitor.

DR. SOLOMON: I think it's an interesting issue, but just to keep our focus on what's before

us.

DR. OLIVER: It helps me think through it because the issue is all of us being on the fence with the safety, what more information would we need that would change our mind one way or the other? That's what I was trying to think through.

DR. SOLOMON: Okay. Jen?

DR. MAYNARD: Just one clarification. In the voting question number 6 regarding the safety profile, there is a sub-bullet about --

DR. SOLOMON: What other data --

DR. MAYNARD: -- if additional data, what data. So we would welcome input about that issue if you do think additional data is needed.

DR. SOLOMON: Should we have that discussion now?

DR. MAYNARD: No. I think you can have it in that question, but just to know, it will come up again about that issue.

DR. SOLOMON: Thanks.

DR. MAYNARD: Thank you.

DR. SOLOMON: Jen?

DR. HORONJEFF: I think to comment on what was said before about we already have other therapies in this IL-6 bucket -- and I say bucket because we're kind of asked to look at it maybe as something a little bit different but within the same capacity.

So hearing back to what some of our speakers prior had say, that if I'm feeling these other biologics, could this be the one; and what Dr. Becker was saying about like an N of 1. So could that actually be what does it for somebody, yet at the same time, it falls under the same IL-6 category.

So I feel conflicted about the same aspect of could that be the something that does it for those individual patients that might not have responded to the other IL-6. But at the same time that's what sponsor was trying to clarify, how are we supposed to look at this, as a new pathway or the same? So that's what I'm still kind of hung up on as well.

DR. SOLOMON: Maria, and then we'll come

back to you.

DR. SUAREZ-ALMAZOR: Actually, I just wanted to go back to what you said a minute ago, that one should only consider what we have been shown. But I think if we only consider that, I mean, it's not really looking great. I think what makes it look better is that we are thinking, well, the placebo looked better than for other drugs, and this and that. But if we actually look at what was presented, it's not really looking that great I would say.

DR. MEISEL: As a rheumatologist, anybody here who is a rheumatologist, if a patient failed one of the other IL agents, would you consider putting a person on this drug as let's try that and see if it's the one, or would you say this is a class effect, they failed the one IL-6 agent, and we have to go to something totally different?

DR. SOLOMON: Are we allowed to talk about this?

(Laughter.)

DR. SOLOMON: I mean, it seems like -- it's

an interesting hypothetical.

DR. MEISEL: Because I think that sort of drives the question you had over there about is this the N of 1, but we have these other alternatives.

DR. SOLOMON: We can discuss it --

(Laughter.)

DR. SOLOMON: -- but you can't suggest how you might vote on that issue, but we can discuss it. Thank you.

DR. FELSON: David Felson. In fairness, the sponsor presented data on this in previous tocilizumab-treated patients versus non in the 3003 trial, and showed that there was an effect that was similar to those who hadn't received tocilizumab. So it didn't look necessarily like a class effect.

The question more is what's the level of effect we're talking about here. So I guess I ask the sponsor once again, do you actually have -- so we're talking about the use of this -- most likely, almost certainly -- in those who have failed other biologics. And everybody keeps saying I wonder if

this is the one.

Well, then the question is, in those who have failed biologics, were there people who actually achieved remission on this therapy compared to placebo, and does the sponsor --

DR. SOLOMON: So I do want to point out that we're talking -- it's an interesting point, and we haven't been shown those data. But we are talking about safety.

DR. FELSON: Oh, sorry. But Steve asked the question of would you use this in someone who failed tocilizumab or another IL-6 inhibitor, and the sponsor showed data supporting that.

DR. SOLOMON: Yes. No, I think that's a good point.

DR. SUAREZ-ALMAZOR: Can I clarify something? I believe -- and the sponsor can say -- that the sponsor said that these were not people who had actually failed tocilizumab because of lack of efficacy.

DR. SOLOMON: We don't know that. Yes, that's a very good point. They did say that.

Thank you for clarifying.

Any more -- Dr. Becker?

DR. BECKER: I think that reining back into safety with the imbalance in all-cause death data that has been presented here, it would be really hard for me to use this as the next line of therapy if someone failed a DMARD, which is the indication that the sponsor's asking for, any DMARD, not a biologic DMARD, not a different class biologic, but any DMARD.

It would be pretty unlikely for me to choose this agent with that risk profile, and that to me says it all. I mean, that to me makes me worry that the safety of this is still in question too much for me to take that risk.

DR. SOLOMON: Okay. I think we've had a lot of good discussion. Before we get to voting, there is a question 5, another discussion question, discuss the dose selection for the phase 3 program. So hold the safety issues in your brain, and we'll come back to vote on that in a minute, but just to talk about the dose selection for the phase 3

program.

We had a pretty good discussion about that this morning. In the phase 2, it was a small study, 30 people per arm with different dosages. There looked to be some separation on a binary outcome of did you reach ACR20 or not, and then when we got to the phase 3, the differences between the two doses selected seemed to go away.

David, do you want to expound?

DR. FELSON: Yes. I guess I was listening to the FDA presentation, I think Mark or somebody, on the requirement that the phase 2 primary outcome be the same as the anticipated phase 2 outcome. I don't remember who talked about that. Oh, sorry. Yes.

I was trying to figure out why you required that. In phase 3, you usually require a binary outcome, and that drives a lot of the sample size consideration in important ways. You don't have that sample size issue in phase 2 outcomes, and therefore you're underpowering your ability to select the right dose.

Why don't you modify that a little bit, if you can, to allow for continuous outcome for phase 2, or an ordinal outcome? If you're going to require an ACR20 for the phase 3 outcome, why don't you require an ordinal phase 20, 50, 70? It has been published, it's validated. It was an outcome for the phase 2, and then you'll have more information and be able to make a more thoughtful, informed decision about what the right dose is rather than limiting yourself.

In the 30 patients, there was a difference by -- it was like 7 versus 8 patients. It just wasn't robust, and it wasn't clear that 15 milligram q4 was the right choice. And it was sort of because you were limiting yourself in terms of the amount of information you were getting.

DR. SOLOMON: Just before we go off on this tangent, is this a useful part of the discussion? Yes? Okay. Good.

DR. PISAL: Dipak Pisal, FDA. So when we were discussing about the phase 2 studies, we're talking about both continuous endpoints and

dichotomous endpoints, ACR20, ACR50, ACR70 as you mentioned, that did show the differences between all of those groups.

So the main point, which now we look at retrospectively, if we look at the dose-ranging studies with the benefit of hindsight, the proposed doses, 50 milligrams every 4 weeks and 100 milligrams every 2 weeks for phase 3, were reasonable. As all doses, including even the lowest dose, which was 25 milligrams every 4 weeks, showed a pretty good response.

However, in light of the safety issues that we have been discussing, we went back to look at these dose-ranging studies, and what we are asking the committee to discuss is how close are we to safety issues with these doses, and is it worth exploring the lower dose that might offer a better safety profile?

Now, answering another question which you posed, can we really go for the binary endpoints in phase 2 as well, that's up to the committee to discuss.

DR. FELSON: This is David Felson. I'm not sure you can get adequate safety data from a phase 2 trial given the sample sizes you were talking about. I don't think you can know that. I think you --

DR. PISAL: Phase 2 is not the forum to really get that data anyway. But the point I mentioned in the presentation, that if we look at the safety lab parameter values, which are very sensitive, we did not see any dose response in phase 2. And the signal which we see in phase 3, you really can't pick up in phase 2.

DR. SOLOMON: Dr. Chowdhury?

DR. CHOWDHURY: Yes. I just wanted to respond back -- I'm Dr. Chowdhury -- to Dr. Felson's comment regarding us asking for ACR20 or ACR based on the dose ranging. Actually, we don't do that, and we leave it up to the investigator or sponsor to see what is reasonable for a dose-ranging study. In fact, in our guidance for rheumatoid arthritis, we even put a hint to us using a continuous endpoint such as DAS, and we

look at all of these. So that was really the response to your question.

Going back to the reasoning of this dose ranging, not necessarily applicable here, in some situations, small molecules perhaps, it can come in that a safety signal if you see may be dose related, and in some situations it may be a class effect. So here, that's where the dose ranging comes in, is it dose related or is it something which is a target? We do not know, and we are not even hinting that a lower dose, lesser frequency, could be safer. We simply do not know.

What we said multiple times, based on the limited phase 2 program, what the company chose, we agreed to it. It looked reasonable. And that brings up the later question, this phase 2/phase 3 is perhaps some sort of an artifact. With 30 patients, how can you make a safety assessment? You really cannot. So the company did the right thing, put multiple doses in the phase 3 program, and it did not pan out what was expected out of phase 2, which is not a surprise either.

DR. SOLOMON: I think an interesting corollary is looking at the phase 3 program, there wasn't a clear dose response for adverse events. So it's not obvious that if you went down on the dose that we would see better safety. Again, I'm speaking --

DR. CHOWDHURY: Yes, that is exactly the point, that if you had an expectation going into the two dosing, which is 4-fold difference normally, and I mentioned earlier, exposure-wise, 6-fold difference -- anyway, the company's expectation was that it would separate out. And the common sense would be that, yes, it's a reasonable dose ranging. It did not separate out.

So we're not just saying that a lower dose is the solution, which we don't have any data to say that, even in the phase 2 program as I mentioned earlier. Going back all the way to 25, the laboratory parameters, which you can assess with 30 patients, it looked the same all across the doses.

So is it a target effect or is it a dose

effect? We do not know. Or could it be entirely an artifact? The mortality may be an artifact, but the laboratory parameters and other parameters is something that we are bringing up for you to opine on.

DR. SOLOMON: Any more comments about the dose selection?

(No response.)

DR. SOLOMON: Okay. Let me just try to summarize before we go to the voting question. The discussion on question 4, which was regarding safety, Jen had mentioned a patient death related to infection and tried to balance that against the availability of a new agent versus the potential for new adverse events, and the fact that patient labels are so complicated to really understand for even educated health-literate patients.

Erica really I think raised the issue whether we could really understand safety from the data as they've been presented, even after they've been presented in several different methods.

Scott talked about the --

DR. WALDMAN: Residual uncertainty.

DR. SOLOMON: -- the residual uncertainty even after we've got this far. I think Beth talked about the consistency of the adverse events, if this was chance, we would expect to see something more random as opposed to a pattern.

Michael wondered about off-target issues and whether we could monitor and assess for potential safety signals as they're occurring and raise the issue of experienced clinicians versus once it's out on the market.

Diane raised the issue, again, of selection criteria, which I think is an important one to keep note. The mechanism of action not being new was raised by Mara. Sean reminded us to keep our focus on what's before us with this package, the sirukumab data, and Maria talked about the mechanism again.

The hard to choose this drug perhaps in the setting of the mortality difference was raised by Mara. We talked about dosing just now, the phase 2 versus phase 3, and really not seeing this clear

dose gradient effect.

So with that, maybe we'll move on now to the voting question. This is question 6. Is the safety profile of sirukumab adequate to support approval of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs?

So again, yes would be, yes, it is safe, the safety profile is adequate. No would be it's not. And then I think after we take a vote, we'll then discuss what data would be needed regarding safety.

DR. WEISMAN: Clarification?

DR. SOLOMON: Please.

DR. WEISMAN: So this is the sponsor's proposed indication, that it's for inadequate response to one or more DMARDs. That could just be methotrexate or it could be a whole bunch, including biologic. So it's the broad --

DR. SOLOMON: Yes.

DR. WEISMAN: -- indication. And that's what the vote is for at the moment.

DR. SOLOMON: Yes.

DR. WEISMAN: Okay.

(Voting.)

DR. SOLOMON: Has everyone voted?

DR. BAUTISTA: The vote is now complete. I will now read the vote into the record, 2 yeses, 11 nos, zero abstentions.

DR. SOLOMON: As we've done before, let's start on the far right. Maybe, David, you could read your vote into the record, and if you want to make comments about why you voted.

DR. FELSON: Okay. This is Dr. Felson. I'm not sure whether the safety signal is of concern or not. I don't think there's enough data here to know that. It's concerning, and it may be just noise, but it may also be real. And I'm not willing to let it out or I'm not willing to be supportive of the notion that it's safe enough to take its place along with other biologics.

DR. SOLOMON: And how did you vote?

DR. FELSON: I voted no.

DR. SOLOMON: Thank you.

DR. BRITTAIN: Erica Brittain. I voted no. It was a very close call for me. I do think there's a real argument to be made about the bias in the analysis that shows the difference or that shows some possibility of a difference. On the other hand, I just couldn't get past feeling uncertain. And when we're talking about mortality, it's hard to dismiss that.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no. I think our first responsibility is to do no harm, and as has been stated already, there are too many uncertainties.

DR. WEISMAN: Michael Weisman. I voted no because what was in front of me was a very broad indication. If the indication was biologic non-responders or inadequate responders, I would have voted yes. That's the fence, and that's the cut-point that disturbed me, and that's the reason for my vote.

MS. ARONSON: Diane Aronson. I voted no because of the issues around the rate of death and serious adverse events and the lab abnormalities.

DR. HORONJEFF: Jennifer Horonjeff. I also voted no, and I echo what Dr. Weisman was saying, that I would like that to be an option for people but not as the way the indication was structured as having failed one or intolerant to one. So I would have perhaps consider it had it been worded differently.

DR. KATZ: James Katz. I actually voted yes because this drug doesn't scare me any more than all the other drugs that I use. I'm very scared by all the biological agents, and this is no different.

DR. BECKER: This is Mara Becker. I voted no, and in light of all those comments, that's exactly it. I think once you get to the point of utilizing a biologic agent, any agent, you increase your risk, of course, and you have those conversations. And my fear was someone may be going to this early in the course and that risk-benefit ratio being outweighed.

Mortality is final, so even though much of that mortality was cardiovascular risk, and we hope

that we'd be able to identify that and recognize those people that are at risk, it's too final for me at this point, so I voted no.

DR. SOLOMON: This is Dan Solomon. I voted no based on not feeling confident about the safety of this drug. It may very well be very similar in safety to other agents. The trial design and the analyses, really inconclusive in my mind. I think it will be good to potentially have more data, and we can have a discussion about what data would be useful.

DR. WALDMAN: Scott Waldman. I'm embarrassed to say I hit the wrong button.

(Laughter.)

DR. WALDMAN: It's muscle memory, and I went for the blinking light. I actually wanted to vote no. So if that could be changed, I would appreciate that. Sorry.

I voted no because there is residual uncertainty. I don't think we have enough information to make an informed decision in favor of the safety of the patients, and I think we need

more information.

DR. JONAS: Beth Jonas. I voted no. Again, I think that there is real uncertainty around the data. And it's certainly possible that this is related to bias, but I think that we don't have enough information to make that decision, so I think we need more data.

DR. OLIVER: Alyce Oliver. I voted no. I think the mortality risk is concerning. I appreciated the FDA putting the definitions of denial up there. I feel that there's insufficient data so far, and I agree that the indication is too broad given the potential risk of the drug.

DR. MEISEL: Steve Meisel. I voted no, and I fully acknowledge this may be very unfair to the applicant because this could all be statistical artifact. The fact of the matter is the signals are there, and we haven't yet found a way to disprove those signals. So in the absence of knowing it's safe, I think we go to that question number 3, or regulation number 3 or 4 that was on that slide that says if you don't know, then you

vote no.

DR. SOLOMON: Okay. I think we want to come back to discuss -- because we voted that it was not safe -- the safety profile was not adequate, what data are needed. I'll start off that discussion, but I'm sure lots of other people have input here.

Again, I think while this could be a play of chance, the mortality issues were very concerning, and the intermediate endpoints on the way towards mortality, serious infection, CV risk, bowel perforation, are obviously concerning. There would need to be some way of having a fair comparison. Again, whether that's related to an active comparator or a placebo I think is a longer conversation. But long-term outcomes data are what we need with a clear comparator. And again, the designs, we could spend a lot of time talking about designs, but I'm not sure if that's relevant right now.

Who else has opinions?

DR. BRITTAIN: Maybe I'm not really answering the question right, but I still wonder if

there is more analysis that can be done of the current data. Again, I brought up what I think is the right intent to treat through Kaplan-Meier. I would be interested in seeing that, where everybody is censured at the point of the re-randomization and if there's anything that can be done with stratifying by important covariates of mortality, baseline covariates of mortality.

So I guess I haven't completely lost hope that there couldn't be some new angles of looking at the mortality. I don't have a lot of hope in that, but I think it should be explored. I'm kind of worried about how to do this, the new data. As was brought up, I don't know what's really the longest placebo period that would be allowable, the comparison to placebo.

DR. SOLOMON: Yes. I don't know. Alyce, do you want to -- somebody raised the point. Who raised the point? It was Scott and then Alyce about active comparators here, and perhaps that would allow us a non-inferiority design with active comparators around safety that would be -- there

have been other safety trials, non-inferiority safety trials done, and that could be a design that would be useful to provide such data.

DR. WALDMAN: I would take comfort in a study -- and this may be naive on my part, but I would take comfort in a study that compared an accepted, approved IL-6 antagonist, one of the two, to this agent, where this agent performed in a non-inferior fashion from an efficacy perspective and performed similarly in terms of safety. Then I would take comfort in the fact that this was safe and effective, at least as safe and effective as what's out there right now and approved.

DR. CHOWDHURY: I think there are some discussions going on regarding what trials one would want the industry to do, and you are bringing up some interesting points for us to hear, which is very, very useful. We also internally thought about it, what a trial could actually potentially look at in terms of powering and sample size, exactly the line that we are talking about here. Perhaps it may be of interest to the

committee, and if it is, then we can show some power calculations on that.

DR. SOLOMON: Sure.

DR. LEVIN: This is Greg Levin, FDA. Can you put up backup slide 152? These pre- or postmarketing safety trials are often designed to have adequate power to rule out a certain magnitude of increase in risk for a particular adverse event of interest.

What this shows, in the different columns, you are varying those different margins. For example, 1.25, the trial would be designed to rule out a 25 percent increase in the risk of whatever event you are targeting.

In these trials, the power is driven by the number of events that are observed rather than the sample size. So you can see, for example, for a trial designed to rule out a margin of 1.25, if there's truly no difference, you would require 631 events to have adequate power under no difference, and for a margin of, say, 1.4, 278 events.

What's shown below is the number of

person-years of follow-up time that you would need, and that's a function of the underlying baseline rate of the event on the control arm. For example, for a margin of 1.25, if there was a true underlying event per 100 person-years of, say, 1.3, you would need just under 50,000 person-years, whereas with a margin of 1.4, more like 21,000 in the bottom right.

The way you would get that would be following -- for example, with 21,000 person-years, you would need to follow, for example, 5,000 patients for an average of 4 years. So this isn't the number of patients; this is the person-years of follow up. So it's a function of both, the number of patients and the follow-up time per patient. If there are any questions on that, I'm happy to address them.

DR. SOLOMON: So what does that mean?

(Laughter.)

DR. LEVIN: Well, I'll leave that to you all.

DR. BECKER: It means we won't do that in

pediatrics.

DR. SOLOMON: Yes. Well, I mean, I think that's the dilemma, the active comparators have -- non-inferiority designs with active comparators quickly blow up to very, very large studies, even if you broaden the margins pretty wide, and they become hundreds of millions of dollars in expense and unlikely to be carried out.

DR. WEISMAN: A clarification question. Greg, you need to defend this a little bit better. This is not an open observation cohort. These are people that prospectively you enroll and follow with very careful follow-up, no loss to follow-up, et cetera.

What are you talking about here? Describe this as -- is this in terms of a clinical trial type set-up or prospectively enroll patients, or is this an observational cohort of patients in a database where there's a lot of sloppiness, and loss to follow-up, and all that?

DR. LEVIN: I think that's a slightly different question. All this is showing is the

numbers of events you would need for adequate power to rule out a specific margin. Theoretically, that kind of data could be collected from either a randomized clinical trial or an observational study, although you would obviously be more concerned, if it was collected for an observational study, that there's bias in those comparisons. And that while your confidence interval might suggest you've ruled out that margin, in truth you haven't ruled out a causable effect as big as that margin.

Most often, we've used randomized clinical trials to rule out levels of risk of this magnitude, these kind of small to moderate increases in risk, because we may be concerned that observational studies, we may not have the reliability of ruling out those magnitudes of risk.

As you said, how reliable those results would be at the end of the study, obviously we would look at things like loss to follow-up, and missing data, and things like that. But these are simple sample size calculations of the number of events and the number of person-years you would

need to have a certain amount of power in a study.

DR. SOLOMON: Before David, Janet, did you want to make a comment?

DR. MAYNARD: Yes. I think just to follow up on that, this was just to give a sense of the size of the study that we were thinking about. I do think we have concerns with using registry data in order to capture this type of safety signal that we're seeing in this trial, so I think we were thinking about in terms of potentially a trial that would be done, but we thought it would be helpful for your discussions to have a sense of how large that trial may be.

As many of you may be aware, tocilizumab or Actemra does have an active comparator study where they compared tocilizumab and etanercept to gather additional information regarding safety events related to cardiovascular events, and that was presented at the American College of Rheumatology last year. And according to the results of that abstract, there was 3,080 patients who were followed for about 3.2 years.

So we just wanted to give a sense of the size that we were talking about because we think it's helpful as you think about what kind of data you would need to address the safety concerns you're discussing today.

DR. SOLOMON: David?

DR. FELSON: Yes. I guess we're talking about two different study issues. One is if we want to be supportive of a trial that might reassure a committee like this one that the rates aren't 4-fold or twice as great as what we frankly saw in some of that data, even with small numbers, the ratio of 1.4 is too modest I think. I think we're okay with ruling out a doubling of rate, I think.

Then I think the 1.2, 1.3, 1.4 stuff, that's going to -- if the drug is approved and then on the market, that is going to be the observational claims-based data study that we do at a later point with thousands of treated patients. But I think for -- I mean, our concern isn't about a 1.2, 1.3, 1.4 increase in serious infection rate or

mortality. Our concern is about a 4-fold increase or a 2- to 3-fold increase.

I think that's what we need to rule out. I think we're comfortable enough with all these other biologics, where we've seen rates bounce around from study to study a little bit, and we have some comfort and familiarity with that. But what we've seen here today is a rate that's a little bit beyond what we're comfortable with. And it could have been caused by bias or by design issues, but it's beyond that. And I think we want to be reassured that it's somewhere in the realm of the usual bouncing around stuff, which isn't 1.4. It's a bigger number than that.

DR. SOLOMON: Maria, and then Erica, and then Michael.

Did you want to answer that?

DR. LEVIN: That's very helpful. As Dr. Maynard just mentioned about the safety study for tocilizumab, that was designed to rule out a 1.8 margin for MACE, and as Dr. Maynard noted, it had roughly -- can you say the numbers again?

DR. MAYNARD: I have the abstract in front of me, so it had a total of 3,080 RA patients who were randomized and followed for an average follow-up time of 3.2 years.

DR. SOLOMON: So 9,000 person-years across both arms of the study to rule out 1.8.

DR. MAYNARD: Right. So the discussions that Dr. Felson was having in terms of what would you need, that's extremely helpful for us, and that's exactly what we want to hear. So we're not here to say this is the study you should do and this is the size. It's more to get a sense from you of what do you need in terms of data to help assess this risk.

DR. SOLOMON: Maria, Erica, and then Michael.

DR. SUAREZ-ALMAZOR: From a logistics perspective, I think it would be very difficult to recruit patients to a trial like this one. The other one, it's to approve drugs, etanercept and tocilizumab, but here it would be basically telling patients you're going to go into a trial with one

approved drug and a drug that's not approved, and we think that the not approved -- they both have the same efficacy, but the one that's not approved we think has a higher mortality rate. So I don't know the practicality of getting patients.

DR. SOLOMON: Erica?

DR. BRITTAIN: That's a good point. Again, I just want to concur that I agree. I think with these relatively small death rates, that a hazard ratio 2 or 3 might be just fine. When you think about it in the absolute difference respect, on a different scale, it's a fairly small difference in death rate.

Also, I wonder if it could be done in a fairly simple way as a mortality endpoint. I don't know whether it would be -- and you probably just want to do intent to treat, but I'm just thinking it might not have to have all the kind of monitoring that we saw in these other trials, that perhaps it could be a streamline trial so it wouldn't be so cumbersome for patients and so expensive.

DR. SOLOMON: Michael, do you want to weigh in?

DR. WEISMAN: I want to ask the FDA a question. Since there was a 4-fold difference in the doses that were used in this trial, was there any hint that there was a dose effect? I recognize the history of having gotten to those two doses and they may have shot themselves in the foot by having to do it that way, but was there any hint that there was a dose effect in the mortality, if you look carefully?

DR. CHOWDHURY: I'm Dr. Chowdhury here. The answer is actually a no. For the mortality, both the doses were reasonably similar. And not only the mortality other events leading up to mortality, infections, malignancies, and other events for both the doses were actually very similar.

In situations like that, I think we're in a hard place, and so is the industry. Having done a reasonably good dose suppression in a phase 3 program expecting to see a difference, they actually don't. And that's where the dosing comes

in, is it really a dose effect, or is it a class effect, or is it a cyto? [indiscernible] effect. So the short answer is no.

The discussion that we're having here regarding a study where the sample size could be what you're interested in ruling out is actually very helpful for us. The industry's also listening. It is very helpful for them to think about what the committee's thinking is.

The issue about going about and doing a study when you're going in, probably with not an equipoise, is going to be very challenging. I think one is to, in that situation, accept it may be an artifact, and therefore there's an equipoise and you can do a study.

So this is something that is very tricky questions you're bringing up, but industry's hearing it, and I'm pretty sure there will be more discussions around that issue. Thank you.

DR. SOLOMON: Yes. So the question of whether there's still clinical equipoise to ethically enroll patients I think is an important

one. I think we're looking at rare events, which is driving these large numbers, and that's what we're usually looking at with regards to safety without some sort of intermediate endpoints that are continuous or that have a high enough correlation. So I think this is what we're find.

Are there other points that want to be raised? Jen?

DR. HORONJEFF: Jen Horonjeff. I'm thinking both about the ethical standpoint here and also going back to the discussion about the placebo effect that was seen. Perhaps it was stated and I didn't catch it, but what was the protocol to enrolling somebody into the study? Did they have to be discontinued from their prior medication for a certain length of time? What was that? How naive were these patients when they enrolled?

DR. MAYNARD: So in both studies 002 and 003, patients could continue on certain background, disease-modifying, antirheumatic drugs.

DR. HORONJEFF: Okay. So could that explain part of why they seemed to be doing well on the

placebo arm as well?

DR. MAYNARD: In terms of the efficacy results?

DR. HORONJEFF: Yes.

DR. MAYNARD: Yes. I think these people had had an inadequate response to the medications prior to coming into the trial, so even though they continued on them during the trial, they had active disease. So I think the placebo response rates we saw in these trials, we didn't find them inconsistent with what we've seen in other rheumatoid arthritis trials, but I think the discussion today has been interesting about that issue.

DR. HORONJEFF: Yes. And I do think that you would be more apt to -- I'm just putting my vote in here for actually doing a comparative study with tocilizumab or another IL-6. You would be able to recruit more patients, I would imagine, because at least they don't have to be taking a difficult choice. And of course you would have to disclose why you're doing the study. But like we

say, for those people who have failed other options, they may be the ones that would want to enroll in this. So I would just put that in there.

DR. MAYNARD: As a follow-up question, one thing that would be helpful for us when you think about a potential trial is if there is a certain comparator that you think would be reasonable if there was a trial to evaluate the safety concerns.

DR. HORONJEFF: Well, put me on the spot here. It's difficult to say right here, but I do think -- from my own standpoint, I think it would be interesting to look at it with another IL-6, of course to look at the efficacy and safety profiles there. But at least to have another known safety and efficacy standpoint from another approved, I would like to say, biologic just because it would make it more clear and not just talking about or saying an indication for somebody who's failed one or more DMARDs, which could just be methotrexate. So I would certainly want to see it compared to another biologic if not an IL-6.

DR. SOLOMON: Sean?

DR. CURTIS: Hi. Sean Curtis. I guess this clarification I'm going to direct to either Dr. Maynard or Dr. Chowdhury, if that's okay. Regarding this study design we're talking about, just for clarification, this input on the design, is it specific to ruling out major cardiovascular risk for this particular compound, are we talking, or is the FDA considering broader consideration along the lines perhaps in the diabetes division where a certain amount of cardiovascular risk, AKA, 1.8, just sort of ruled our pre-approval?

This study design, the relative risk in the study design size for tocilizumab, that does sort of suggest study designs that rule out a certain magnitude of cardiovascular risk pre-approval, and then additional data. So I'm just in the spirit of openness trying to understand a little bit where this discussion might go or what the FDA's thinking is.

DR. CHOWDHURY: Here, we are actually not necessarily proactively suggesting anything, or saying anything, or asking for anything. It's just

a matter of the committee discussing if safety's not enough, what else can somebody do, and of course the issue is mortality.

So to aid the discussion, we just put this up as what we can call it to have the discussion, which we're having. And the example that Dr. Maynard mentioned with a specific postmarketing trial, that was for a MACE event, so that's entirely different. Here it is just for a general broad discussion, and that's what we are doing here.

So I think we heard about the active comparator. If there are any other comments, it would be interesting for us to hear that.

DR. SOLOMON: Maria?

DR. SUAREZ-ALMAZOR: My understanding is that the FDA is not very keen on adaptive designs, but I wonder if this is a case where an adaptive design with some sort of Bayesian randomization, according to safety signals, would be appropriate.

DR. LEVIN: This is Greg Levin, FDA. Possibly. I think we'd have to answer the

fundamental design questions first about what the objective was, what the margin was, what the comparator was, what the duration was, and then we could talk about whether adapting certain things do or do not have advantages.

Ultimately incorporating adaptations would often be at the discretion of the sponsor about whether they want to incorporate something like that to increase the efficiency of the study or not. So I think we'd have to answer some of the fundamental questions like the choice of the comparator and what the objective of the study was first.

DR. SOLOMON: Erica?

DR. BRITTAIN: So I guess one thing, before embarking on something like this, that would need to be understood is how you're going to handle people who do not respond so you're not in the same situation you were in with the placebo-controlled trial.

Presumably, it wouldn't be as much of a problem, but to some extent, it's still going to

happen. So you'd have to think about how you would handle that before you get too far into this.

DR. SOLOMON: I'm going to suggest that we now close this discussion. There is a schedule to break, but the last point of business for us is the voting question, and it might just be valuable to move from this discussion to question 7.

Are people okay with that?

(Affirmative response.)

DR. SOLOMON: Question 7, I'll read it, and then we'll vote. Do you recommend approval of sirukumab at the proposed dose of 50 milligrams subcutaneously every 4 weeks for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs? And if not, what data are needed? So we'll vote now.

(Voting.)

DR. SOLOMON: Okay. We're complete.

DR. BAUTISTA: I will now read the vote into the record: 1 yes, 12 nos, zero abstention.

DR. SOLOMON: Why don't we start again at the far right with David Felson?

DR. FELSON: Hi. David Felson. I want to compliment Dan on saying sirukumab like it's one of his children. I had no idea how to pronounce it. Sorry to be flippant here.

I think the safety data's a little too uncertain to lump this with all the other biologics that we have, and it makes me uncomfortable voting in favor of approving its use. In a sort of non-descript way for all people who failed second-line drugs, I think that's a step a little bit too far given the data that we currently have.

DR. SOLOMON: David, did you tell us your vote?

DR. FELSON: I did. I voted no.

DR. BRITTAIN: Erica Brittain. I voted no. Again, close call for me because I am sympathetic to the fact that I think there's a real possibility that the difference we're seeing in mortality is the bias. As we already talked about, the efficacy results are very strong, or at least strong in

terms of what they needed to show. But I just cannot completely shake the uncertainty about the mortality.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no also because of safety concerns. Again, I would have been more enthusiastic if this was a completely novel mechanism of action, but in view of the existing IL-6 receptor antagonist, I was less enthusiastic about this drug.

DR. WEISMAN: Michael Weisman. I voted no because of the too broad an indication and the uncertainty of the safety signal.

MS. ARONSON: Diane Aronson. I voted no because of the safety signals.

DR. HORONJEFF: Jen Horonjeff. I voted no because of the safety signals, but also because of the broadness of the indication.

DR. KATZ: James Katz, and I voted yes.

DR. BECKER: Mara Becker. I voted no due to the imbalance in the all-cause mortality and broad indication.

DR. SOLOMON: Dan Solomon. I voted no.

DR. WALDMAN: Scott Waldman. I voted no.

DR. JONAS: Beth Jonas. I voted no.

DR. OLIVER: Alyce Oliver. I voted no for the same reasons stated when we discussed safety concerns.

DR. MEISEL: Steve Meisel. I voted no.

DR. SOLOMON: Well, we've gotten to the end of the meeting and went by that break. We're now at the adjournment. Before we adjourn, are there any last comments from the FDA?

DR. MAYNARD: This is Janet Maynard. I just really wanted to thank everyone for their great discussion today. It was extremely helpful, and we really appreciate all the insightful comments. And we will see many of you tomorrow.

Adjournment

DR. SOLOMON: Great. Okay. So please take all your personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so they may

be recycled, and we will now adjourn the meeting. Thank you very much.

(Whereupon, at 3:32 p.m., the meeting was adjourned.)