FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC)

Thursday, August 3, 2017

7:59 a.m. to 12:12 p.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

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P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. SOLOMON: Good morning. I'm Dan Solomon, and 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 would also like to identify the FDA press contact, Theresa Eisenman. Theresa, can you raise your hand if you are present?

My name is Dan Solomon, and I'm the chair of the Arthritis Advisory Committee, and I will now call the August 3, 2017 meeting of the Arthritis Advisory Committee to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left, and then we'll follow.

DR. CHOWDHURY: Good morning. I'm Badrul Chowdhury. I'm the director of the Division of Pulmonary Allergy and Rheumatology Products.

DR. MAYNARD: Good morning. I'm Janet

Maynard. I'm clinical team leader in the Division of Pulmonary Allergy and Rheumatology Products.

DR. NAIR: Hi. I'm Raj Nair, medical officer, Division of Pulmonary Allergy and Rheumatology Products.

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

DR. ROTHWELL: Rebecca Rothwell, mathematical statistician, Division of Biometrics II.

DR. MEISEL: Steve Meisel, medication safety officer, Fairview Health Services in Minneapolis.

DR. OLIVER: Good morning. Alyce Oliver. I'm a rheumatologist at the Medical College of Georgia.

DR. JONAS: Good morning. I'm Beth Jonas from the University of North Carolina at Chapel Hill. I'm a rheumatologist.

DR. SOLOMON: I'm Dan Solomon. I'm a rheumatologist and clinical scientist at Brigham and Women's Hospital in Boston.

DR. BAUTISTA: Good morning. Phil Bautista,

acting designated federal officer for this committee meeting.

DR. BECKER: Hi. Mara Becker. I'm a pediatric rheumatologist at Children's Mercy in Kansas City and in the Division of Clinical Pharmacology.

DR. KATZ: I am James Katz. I'm a rheumatologist at the NIH.

DR. HORONJEFF: Jen Horonjeff, a patient-centered outcomes researcher at Columbia University Medical Center, also a patient with rheumatic diseases serving as the consumer representative.

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

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

DR. SUAREZ-ALMAZOR: Good morning. I'm Maria Suarez-Almazor. I'm a rheumatologist at the University of Texas MD Anderson Cancer Center.

DR. BRITTAIN: I'm Erica Brittain. I'm a

statistician at National Institutes of Allergy and Infectious Diseases, NIH.

DR. CHUNG: I'm James Chung. I'm the industry representative. I'm a rheumatologist and an employee of Amgen.

DR. SOLOMON: Thanks. 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. 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.

Now I'll pass it to Phil Bautista, who will read the conflicts of interest statement.

Conflict of Interest Statement

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 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, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves supplemental new drug application, or sNDA, 203214, supplement 17, for Xeljanz, tofacitinib, and 208246, supplement 3, for Xeljanz XR tofacitinib extended-release tablets, submitted by Pfizer, Incorporated for the treatment of adult patients with active psoriatic arthritis.

The committee will discuss the efficacy and safety data and benefit-risk considerations. This is a particular matters meeting during which specific matters related to Pfizer's sNDA 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 FDA's invited industry representative, we would like to disclose that Dr. James Chung is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Chung's role at this meeting is to represent industry in general and not any particular company. Dr. Chung is employed by Amgen.

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

relationships that they may have with the firm at issue. Thank you.

DR. SOLOMON: We will now proceed with the FDA's opening remarks from Janet Maynard.

FDA Introductory Remarks – Janet Maynard

DR. MAYNARD: Good morning. My name is Janet Maynard. I am a rheumatologist and clinical team leader in the Division of Pulmonary Allergy and Rheumatology Products. I would like to welcome you to the Arthritis Advisory Committee meeting for new drug application or NDA 203214, supplement 17, and NDA 208246, supplement 3 for tofacitinib and tofacitinib extended release for the treatment of adult patients with active psoriatic arthritis. I will provide NDA's introductory remarks for this Arthritis Advisory Committee meeting.

Psoriatic arthritis is a chronic progressive inflammatory arthritis associated with psoriasis. Psoriatic arthritis can result in permanent joint damage and disability. Multiple therapeutic options have been approved for psoriatic arthritis over the last 15 years.

Tofacitinib is a Janus kinase inhibitor currently approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

The proposed indication is the treatment of adult patients with active psoriatic arthritis. The proposed dose for psoriatic arthritis is the same as the approved dose for rheumatoid arthritis.

As background, tofacitinib immediate release was initially approved on November 6, 2012 for the treatment of moderately to severely active rheumatoid arthritis. An extended-release tablet was subsequently approved in 2016.

In October 2015, the agency issued a complete response for tofacitinib for the treatment of moderate to severe plaque psoriasis. A complete response means the agency did not approve tofacitinib for moderate to severe plaque psoriasis. Recognizing that patients with psoriatic arthritis can have concomitant psoriasis, the focus of today's meeting is on the proposed

indication of psoriatic arthritis.

This slide provides an overview of safety considerations associated with tofacitinib as described in the currently approved prescribing information. Tofacitinib has a boxed warning for serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections. In addition, tofacitinib has a boxed warning for malignancy, including lymphoma and other malignancies.

Tofacitinib has warnings and precautions related to serious infections, malignancy, GI perforations, laboratory abnormalities, and vaccinations. Dr. Nair will provide additional information regarding the safety of tofacitinib during his presentation later this morning.

This table provides an overview of the tofacitinib clinical development program for psoriatic arthritis. Additional details regarding these studies will be reviewed during FDA's presentations this morning.

Briefly, study 1091 was a randomized double-blind 12-month study of tofacitinib, placebo, and adalimumab. Study 1125 was a randomized, double-blind, 6-month study of tofacitinib and placebo. Study 1092 was an open-label extension study of 1091 and 1125.

I will now highlight some key efficacy and safety considerations to provide a framework for the committee's discussion. We will start with efficacy considerations.

The submitted data provide evidence of tofacitinib's efficacy for signs and symptoms and physical function in psoriatic arthritis. However, the totality of the data does not provide substantial evidence that tofacitinib has an effect on radiographic progression.

It is important to note that evidence of radiographic benefit has not been considered necessary for approval for drugs that treat psoriatic arthritis.

In general, the safety profile of tofacitinib in psoriatic arthritis appears

consistent with the known safety profile of tofacitinib and rheumatoid arthritis. Tofacitinib was associated with adverse events related to immunosuppression, such as serious infections in herpes zoster.

In the psoriatic arthritis clinical program, there were also malignancies, major adverse cardiovascular events, gastrointestinal perforation, and laboratory abnormalities.

In this framework, there are several issues we hope the committee will discuss today. These include the efficacy of tofacitinib for the treatment of active psoriatic arthritis and the safety of tofacitinib in psoriatic arthritis. Lastly, the committee will discuss the overall risk-benefit and approval recommendation for psoriatic 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 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: Thanks, Dr. Maynard. 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 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 interests 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 Pfizer's presentations.

Applicant Presentation - Nancy McKay

MS. McKAY: Good morning, Mr. Chairman, members of the advisory committee, and members of the FDA. Thank you for the opportunity to present the data that support the approval of tofacitinib, a new treatment option for patients with psoriatic arthritis.

My name is Nancy McKay. I'm the U.S. regulatory lead for tofacitinib for psoriatic arthritis. I'll briefly describe tofacitinib and the development program for psoriatic arthritis. Following my presentation, Dr. Philip Mease, a rheumatologist from the University of Washington, will describe the burden of disease of psoriatic

arthritis, a complex disease which causes morbidity and mortality and disrupts the lives of patients. He'll show that there's a need for new therapy with a different mechanism of action.

Then Dr. Keith Kanik will present the efficacy data that demonstrate how tofacitinib meets this need by providing improvement across the spectrum of disease. Following Dr. Kanik, Dr. Graham will show that the established safety profile of tofacitinib reflected in the psoriatic arthritis program has no new identified risks, then Dr. Jones will describe a program to manage the known risks and continue to assess for any new ones.

Finally, Dr. Corbo will show that the benefit-risk profile of tofacitinib is positive for the treatment of psoriatic arthritis, offering a new important option for patients with PsA.

While biologic therapies are commonly used to treat psoriatic arthritis, tofacitinib is an oral small-molecule therapy. This is a novel approach to the treatment of psoriatic arthritis.

It's a JAK inhibitor that reversibly inhibits the Janus family of kinases. In that way, it interferes with the signaling of cytokines important to the pathogenesis of psoriatic arthritis.

In developing tofacitinib for psoriatic arthritis, we specifically sought to develop an effective oral drug with a manageable safety profile and efficacy similar to TNFi inhibitors, which are parenteral biologic agents.

Because of its unique mechanism of action and its oral administration, tofacitinib could be a valuable new treatment option for patients with unmet needs, building on the extensive clinical experience with Xeljanz and RA, and clinical trials, and other indications.

Xeljanz has been extensively studied with phase 3 clinical development programs, including rheumatoid arthritis, psoriasis, psoriatic arthritis, and ulcerative colitis. Overall, it's estimated that over 20,000 patients have participated in the tofacitinib clinical

development program with patients exposed up to 9 years. The total estimated postmarketing exposure is in excess of 83,000 patient-years.

Specific to psoriatic arthritis, the safety of tofacitinib is based on a clinical development program that consists of 783 PsA patients that have been exposed to tofacitinib, with a total of 775 patient-years of tofacitinib exposure.

The extensive clinical program has resulted in a number of regulatory applications. Tofacitinib was first approved for RA in 2012 with a supplemental approval for the extended-release formulation in 2016. Tofacitinib tablets are now approved for RA in more than 80 countries worldwide, including the U.S., Canada, Europe, and Japan.

Tofacitinib has also been developed for other indications. In response to Pfizer's application for psoriasis, FDA's Division of Dermatology and Dental Products issued a complete response letter, requesting additional data to further support the benefit-risk of tofacitinib in

psoriasis.

While the overall safety profile in psoriasis is highly consistent with that in RA, the dermatology division requested additional information on long-term safety events of interest, including data on cardiovascular events, opportunistic infections, and malignancy.

In consideration of the complete response letter, the time needed to collect the data and the advent of transformational treatment options in psoriasis, Pfizer made a decision to withdraw the application for psoriasis in 2016 to focus on programs in psoriatic arthritis and other indications.

Supplemental applications for psoriatic arthritis and ulcerative colitis were submitted in February and May of this year, respectively. Events of interest included with the psoriatic arthritis application, which include RA, psoriasis, and psoriatic arthritis events, will be described by Dr. Graham during her safety presentation.

Xeljanz's application for psoriatic

arthritis shows that 5 milligrams BID of tofacitinib in psoriatic arthritis has shown efficacy consistent with biologic DMARDs in the TNFi naive patients and similar efficacy in TNFi inadequate responders.

The safety profile of tofacitinib, including that in psoriatic arthritis patients, is well-characterized, stable, and manageable. It's informed by a large and growing safety database with consistency between real-world and clinical safety data.

The benefit-risk profile of tofacitinib 5 milligrams BID for psoriatic arthritis is positive and is based on substantial clinical evidence. Based on these results, the proposed indications for the treatment of adult patients with active psoriatic arthritis, the recommended dose of Xeljanz is 5 milligrams, twice daily used in combination with conventional synthetic DMARDs.

I'd now like to present Dr. Philip Mease. Dr. Mease is the director of rheumatology research, Swedish Providence St. Joseph's Health Systems, and

clinical professor, University of Washington School of Medicine in Seattle. Dr. Mease will be giving a physician's perspective of psoriatic arthritis, including the unmet medical need. Dr. Mease?

Applicant Presentation - Philip Mease

DR. MEASE: Thank you, Nancy.

Mr. Chairman, members of the advisory committee, and members of the FDA, I am pleased to be here today to represent my physician's perspective on the use of tofacitinib and an overview of the unmet need in psoriatic arthritis. These are my disclosures.

I have had over 35 years' experience as a clinical rheumatologist and am a clinical professor at the University of Washington in Seattle. My clinical experience with tofacitinib in treating RA patients has been since its approval in November 2012. My research experience includes the design, conduct, and publication of the majority of psoriatic arthritis clinical trials, including the first trial of TNF inhibitor therapy and PsA, published in the year 2000.

My research involvement with tofacitinib has been as an investigator in five RA studies and in the design conduct and data interpretation of this psoriatic arthritis program. I have a leadership role in various relevant committees and working groups related to research and education about psoriatic arthritis, as you can see on this slide.

Psoriatic arthritis is a distinct disease which is characterized by a number of different clinical manifestations. In the U.S., it occurs in up to 30 percent of patients with psoriasis, which is present in 3 percent of the general population.

The most important issue that affects virtually all patients with psoriatic arthritis, including my own patients, is peripheral arthritis, which can be quite disabling and painful, and untreated, can result in irreversible joint destruction.

Sustained pain and fatigue, physical dysfunction, and unpredictable disease flares substantially change the lives of my patients who are afflicted in their prime work and family-

raising years.

A second issue is enthesitis, affecting tendon and ligament insertions into bone, which typically occurs in about half to two-thirds of PsA patients, both in my own experience and in large clinical cohorts.

Inflammation and pain at entheseal sites can be difficult to treat, takes longer to resolve, and can be particularly disabling. When I have a patient hobbled by Achilles enthesitis, who wears an orthopedic boot for a long period of time, many aspects of their work and family life are disrupted.

Dactylitis, where inflammation of a whole digit causes a sausage-like swelling, is a biomarker of more intense and severe disease and is pathognomonic for PsA. Spondylitis occurs in approximately half of the patients with PsA, and when present causes significant back pain and work disability. Of course, virtually all patients have skin psoriasis, which can be emotionally handicapping and very embarrassing.

In addition to the disease itself, patients with PsA have increased comorbidities such as cardiovascular disease, depression, and diabetes, and premature mortality, which further adds to the burden of the disease.

The SF-36 is a patient questionnaire that is a measure of quality of life used generically across many different diseases. The domains of the SF-36 are noted here. The purple polygon shows an SF-36 result for a normal individual in the population.

The more shrunken polygon in green, depicting lower or worse score numbers, represents the impact of psoriasis on quality of life, including worse mental health, emotional health, and social function. An even more shrunken red polygon here represents the negative impact of psoriatic arthritis on quality of life. There's even greater impact on physical function, bodily pain, general health, and fatigue than psoriasis.

This picture jives with my experience with patients. Already embarrassed and depressed about

having psoriasis, when PsA later on enters their lives, now is added pain, fatigue, and physical dysfunction, making them even more depressed about the change their lives have taken.

There are a number of treatments available for psoriatic arthritis patients. These include anti-inflammatory medicines and steroids for those with milder disease, commonly followed by other options such as conventional DMARDs, TNF inhibitors, several non-TNF biologics, and targeted synthetic DMARDs, which are all used for PsA.

In contrast to rheumatoid arthritis, most patients end up on monotherapy, largely due to concern by both clinicians and patients about methotrexate toxicity in PsA.

Although conventional synthetic DMARDs are widely used, we do not have much data from randomized clinical trials regarding their efficacy. And what little we do have suggests modest effect on PsA at best.

Many patients have difficulty tolerating these medicines. I can attest to this from my

experience with patients in practice. Further, in several manifestations of PsA, such as enthesitis, dactylitis, and spondylitis, they have little or no beneficial effect.

In terms of biologic DMARDs and targeted synthetic medications, much better results, at least initially, have been achieved, including the goal of low disease activity or remission. However, 36 to 63 percent of patients do not respond adequately initially, and up to 69 percent more may lose response over time or may experience adverse events, which leads them to switch from one medication to another, thus the need for many treatment options and different mechanisms of action.

Here is data from a Danish registry in which patients are being treated with TNF inhibitors for PsA. It demonstrates that the median drug survival on the first TNF is about two years and then patients are needing to switch, presumably because of loss of efficacy or adverse effects.

Then as they switch from the first to a

second or third TNF inhibitor, that time period of effectiveness is even less. Again, this emphasizes the point that patients need to switch to try to regain effectiveness, and they may need a different mechanism of action to switch to.

Furthermore, patient surveys show that more than 50 percent of patients find therapies burdensome either because of the lack or loss of effectiveness or adverse events that I've just mentioned, fear and anxiety of injections, pain and discomfort of injections, or inconvenience, for example having to come into an infusion center or needing to refrigerate medications.

These findings ring true in my experience, since I hear all the time from my patients about these various issues. And these elements that are important for patients, together with the efficacy and safety profile of the available drugs, will in the end lead to a treatment decision.

How does a potential new therapy that inhibits Janus kinase work in psoriatic arthritis? This image shows the time sequence of gradually

progressive joint destruction in a distal interphalangeal joint, on the right-hand side, the classic pencil and cup change that we see in psoriatic arthritis. And certainly in my practice, I've seen patients with horrible destructive disease like this.

Enthesitis, synovitis, and osteitis are demonstrated in this lateral MRI of an ankle. On the right-hand side, an arrow points to light up where the Achilles tendon is inserting into the heel bone, consistent with enthesitis and osteitis, and on the left-hand side, the arrow is pointing to synovial inflammation in the ankle joint. From the patient's perspective, this ankle and heel are painful and causing functional disability. They also often have a nagging concern about progressive structural damage of the joint.

How do we get at treating these various sites of inflammation? This table depicts the various cells and cytokines involved in the inflammatory cascade and various tissue domains of psoriatic arthritis. The third column shows the

cytokines that are activating and maintaining the inflammatory state in these various cells and tissue sites. The last column on the right shows the various cytokines that are produced by these cells and promulgate the inflammatory cascade.

Tofacitinib will directly modulate the signaling of cytokines, shown in red, and tofacitinib has also been shown to indirectly modulate the effect of cytokines noted in blue.

In summary, I have demonstrated to you that psoriatic arthritis is a complex disease with multiple clinical manifestations that have a high impact on patients and result in physical disability and psychosocial distress.

Each patient with psoriatic arthritis is clinically unique. I say to each of my patients that no one is going to present exactly like you because of the variety of clinical manifestations and, therefore, the need to tailor individual treatment approaches.

Thus, there is a need for a variety of types of treatments and mechanisms of action to most

effectively treat each individual patient, especially now that we know that treating to a targeted low disease activity or remission is desirable.

Despite the fact that we have a number of good therapeutic options currently, I've demonstrated to you that patients either do not respond initially, lose effectiveness over time, or may experience adverse effects from current treatments. This leads to the need to have different options available to start with or switch to.

Thus, we need another medication which has a unique mechanism of action and features such as an oral mode of delivery, which many of my patients say they would prefer to take. Such a drug could be tofacitinib, which has a well-characterized efficacy and safety profile, as we rheumatologists have grown comfortable with it over the last many years in treating patients with rheumatoid arthritis. Based on the data I have seen and my experience with patients in the PsA trial program,

it may also provide benefit to various patients with psoriatic arthritis.

I'd now like to turn the presentation over to Keith Kanik, senior director and global clinical lead for the psoriatic arthritis program at Pfizer.

Applicant Presentation – Keith Kanik

DR. KANIK: Thank you, Dr. Mease.

From Dr. Mease's presentation, you understand how psoriatic arthritis is a complex disease that's anchored by peripheral arthritis, the most common presentation of psoriatic arthritis and the focus of psoriatic arthritis drug development.

We powered and designed the pivotal studies for this supplemental NDA to assess efficacy of tofacitinib on peripheral arthritis. Therefore, all patients were required to have at least 3 painful and 3 swollen joints at both screening and baseline study visits.

Although active disease as measured and the other disease manifestations were not required for patients to enter the study, various assessments

were made in those patients who had them. The assessments that remain darkened are the endpoints that will be discussed in this presentation.

All patients participating in the tofacitinib psoriatic arthritis development program had to meet CASPAR classification criteria. These criteria are the criteria used in other psoriatic arthritis clinical development programs. Activity as related to other criteria, including psoriasis, contribute to satisfying these classification criteria, but concurrent active disease in all manifestations is neither mandatory to meet classification criteria nor typical in the clinic.

This is the tofacitinib psoriatic arthritis program design. It consisted of two randomized placebo-controlled pivotal studies and a long-term extension study. Similar study visit schedules up to month 6 were designed to allow pooling of the data.

The primary endpoint of the open-label long-term extension study was safety. Therefore, these data will be discussed as part of the safety

presentation.

Dose-ranging studies done in the rheumatoid arthritis and psoriasis clinical development programs were used to support the choice of tofacitinib 5 milligrams twice daily and 10 milligrams twice daily in those respective phase 3 programs and were used to support the dose choices of 5 milligrams twice daily and 10 milligrams twice daily for this psoriatic arthritis phase 3 program.

I will now discuss study A391091. This study was performed in a conventional synthetic DMARD inadequate responder TNFi-naive patient population and will be referred to as a TNFi-naive study in this presentation.

Define reasons for an inadequate response to conventional synthetic DMARDs with a lack of efficacy or a related adverse event. The primary analysis includes that all patients are analyzed and treated with tofacitinib, the primary efficacy endpoints with the ACR20 response rate, and the change from baseline in HAQ-DI at 3 months.

These primary endpoints were assessed

sequentially as part of a statistical hierarchical plan that was type 1 error-controlled for multiple comparisons. The key secondary endpoints, PASI75 through FACIT-F at month 3, were assessed sequentially in the order shown and controlled for type 1 error.

ACR50 and 70 responses at month 3 and ACR20 pre-month 3 were also controlled separately for type 1 error. In this study, placebo duration was 3 months, and all patients were on a stable background CS DMARD.

For this study, unique design elements included a 12-month duration, the use of blinded adalimumab as an active comparator reference arm, and the collection of radiographs of the hands and feet at study entry in month 12. This double-blind, double-dummy study was designed to estimate the treatment differences between tofacitinib and adalimumab. 422 patients were randomized in the TNFi-naive study. Most patients completed the study. Patients on placebo had higher rates of discontinuation than those on active drug.

I will now discuss the second pivotal study, study A391125. This study was performed in a TNF inhibitor-inadequate responder patient population and will be referred to as the TNFi-IR study in this presentation.

Defined reasons for an inadequate response for two TNF inhibitors were either lack of efficacy or related adverse event. Design elements such as endpoints, endpoint analysis, type 1 error control, and placebo duration were almost identical to the TNFi-naive study. Differences from the TNFi-naive study included a shorter 6-month duration, no active comparator, and no radiographs.

395 patients were randomized in the TNFi-IR study. 394 patients were treated. Most patients completed the study. Patients receiving tofacitinib, 5 milligrams twice daily, had the lowest discontinuation rate.

Patients participating in the two pivotal studies had similar baseline demographics and disease characteristics. These characteristics are consistent with those of patient populations in

phase 3 studies for other approved treatments for psoriatic arthritis.

Patients who were in the TNFi-IR study had a longer mean PsA duration, since typically patients must first have an inadequate response to a CS DMARD prior to using a TNF inhibitor.

At month 3, both 5 milligrams twice daily and 10 milligrams twice daily demonstrated similarly significant improvements in peripheral arthritis as measured by the ACR20 response rate, the first primary endpoint in both studies. For tofacitinib, but not adalimumab, ACR responses were controlled by type 1 error.

Responses to tofacitinib 5 milligrams twice daily were consistent across the two studies in the ACR20. Tofacitinib responses were similar to adalimumab in the TNFi-naive study.

At month 3, both 5 milligrams twice daily and 10 milligrams twice daily demonstrated similarly significant improvements in peripheral arthritis, as measured by the more stringent ACR50 response rate across both studies. Tofacitinib

responses were again similar to adalimumab in the TNFi-naive study.

At month 3 in the TNFi-naive study, both tofacitinib, 5 milligrams twice daily and 10 milligrams twice daily demonstrated significant improvements in the ACR70 response rate relative to placebo. However, in the TNFi-IR study, neither dose achieves statistical significance.

The tofacitinib ACR20 responses at time points through month 3 were type 1 error controlled. Tofacitinib 5 milligrams twice daily in the blue diamond and 10 milligrams twice daily in the orange square demonstrated similar statistically significant improvements relative to placebo, the gray circle, on the ACR20 response at 2 weeks, the first time point in which response was assessed in both studies. Tofacitinib response to the TNFi-naive study were similar to adalimumab in the magenta triangles.

The magnitude of the ACR20 responses continue to increase through the end of the placebo-controlled period at month 3 when the

primary endpoint was measured in both studies. Tofacitinib response in the TNFi-naive study in this time period were similar to adalimumab.

After the 3-month placebo-controlled period, the ACR20 response and all active treatments in the TNFi-naive study continued to increase or stabilize with convergence at four months. Throughout the TNFi-IR study, ACR20 responses for both tofacitinib 5 milligrams twice daily and 10 milligrams twice daily were similar, and note that both studies were analyzed using the non-responder imputation for missing data. Furthermore, patients, investigators, and the clinical study team remain blinded to treatment throughout the completion of both studies.

Significant improvements in physical function for both tofacitinib 5 milligrams twice daily and 10 milligrams twice daily were demonstrated by change from baseline of the HAQ-DI, the second primary endpoint at 3 months in both studies. Tofacitinib responses in the TNFi-naive study were again similar to adalimumab.

Radiographs in the TNFi-naive study were obtained at the beginning of treatment and at 12 months. All patients were on background conventional synthetic DMARDs. Patients were not enriched for risk factors associated with structure progression, and the placebo period was limited to 3 months. Detectible progression was not anticipated in placebo-treated patients.

This prespecified analysis instead compared tofacitinib to adalimumab on the change of the van der Heijde Modified Total Sharp Score for PsA. It was not designed to demonstrate superiority to placebo or non-inferiority to adalimumab.

Structural progression on tofacitinib treatment was not anticipated based on inhibition of structural progression demonstrated in the tofacitinib rheumatoid arthritis development program.

This is the cumulative probability plot of the changes from baseline of the van der Heijde Modified Total Sharp Score for PsA. Most patients on active treatment at month 12 had no change from

baseline. The progressive rates of tofacitinib 5 milligrams twice daily or 10 milligrams twice daily using either a cutoff of 0 or 0.5 were low and similar to adalimumab.

Tofacitinib has effects on psoriatic arthritis disease manifestations beyond peripheral arthritis. About two-thirds of the patients in TNFi-naive and TNFi-IR studies had sufficient body surface area affected by psoriasis at baseline to measure a PASI70 response, the first type 1 error-controlled secondary endpoint in the hierarchical testing scheme.

Both tofacitinib 5 milligrams twice daily and 10 milligrams twice daily were statistically significant in the PASI75 response rate at 3 months in the TNFi-naive study, and these were type 1 error controlled. In this study, tofacitinib 5 milligrams was similar to adalimumab at 3 months and continued to improve.

In the TNFi-IR study, tofacitinib 10 milligrams twice daily but not 5 milligrams achieved statistical significance in the PASI75

response rate at month 3, and the prespecified type 1 controlled testing ended.

Five milligrams twice daily and 10 milligrams twice daily effects on the PASI75 were similar both at 1 month and 6 months. Based upon the overall evidence, both doses of tofacitinib demonstrated efficacy for the treatment of psoriasis.

Enthesitis is a difficult-to-treat manifestation of PsA and contributes to patient pain and inability to function. Patients on tofacitinib 10 milligrams twice daily but not 5 milligrams twice daily in the TNFi-naive study demonstrated statistically significant reduction in the LEI at month 3 and the prespecified type 1 control testing ended.

No further type 1 error testing was conducted. The magnitude of the treatment of X converged for all active treatments at 6 months and continued to improve to month 12 in this study.

Despite the lack of type 1 error controlled in TNFi-IR study, patients treated with either

tofacitinib 5 milligrams twice daily and 10 milligrams twice daily demonstrated reductions relative to placebo at 3 months on the Leeds Enthesitis Index, and the 5 milligrams twice daily demonstrated a reduction relative to placebo at 1 month, the first time point measured. Both doses demonstrated similar improvements at month 6.

Based upon the overall evidence, both doses of tofacitinib demonstrated efficacy for the treatment of enthesitis.

Dactylitis is another difficult-to-treat manifestation of psoriatic arthritis that responds slowly to treatment. Patients treated with tofacitinib 10 milligrams twice daily but not 5 milligrams twice daily in TNFi-naive study demonstrated improvement relative to the placebo and the change in DSS at month 3. The magnitude of the treatment effect converged for all active treatments at 6 months and continued to improve at month 12 in this study.

Patients treated with both tofacitinib doses demonstrated a reduction in the Dactylitis Severity

Score relative to placebo at 3 months in the TNFi-IR study, and both continued to improve at 6 months.

Based upon the overall evidence, both doses of tofacitinib demonstrated efficacy for the treatment of dactylitis.

Patient-reported outcomes in addition to the HAQ-DI in these studies included the SF-36 and the FACIT-F, which measured physical function and fatigue. At month 3, improvements in the SF-36 physical functioning domain and FACIT-F total score relative to placebo was seen for tofacitinib 5 milligrams twice daily and 10 milligrams twice daily in both studies at 3 months.

SF-36 and FACIT-F improvements in TNFi-naive patients receiving either tofacitinib dose were similar to adalimumab.

In conclusion, tofacitinib 5 milligrams twice daily demonstrated efficacy in two well-characterized and important patient populations, TNFi-naive and TNFi-inadequate responders, with efficacy similar to the active

comparator, adalimumab.

Patients treated with tofacitinib 5 milligrams twice daily demonstrated statistically significant improvements in the ACR20 and the HAQ-DI, primary efficacy endpoints at month 3, as well as statistically significant type 1 error-controlled improvements in the ACR50 response at month 3 and on the ACR20 response as early as 2 weeks.

Patients treated with tofacitinib 5 milligrams twice daily had clinically meaningful improvements relative to placebo. They were similar to adalimumab and other psoriatic arthritis disease manifestations such as psoriasis, enthesitis, dactylitis, and patient-reported outcomes of physical function and fatigue. These were significant in the prespecified pooled analysis.

TNFi-naive patients treated with tofacitinib 5 milligrams twice daily had a similar lack of progression to those patients treated with adalimumab.

Based on the totality of the evidence, we have chosen 5 milligrams twice daily as a proposed dose for the treatment of psoriatic arthritis. There were insufficient clinically meaningful additional benefits in patients treated with 10 milligrams twice daily relative to the 5 milligrams twice daily to justify proposing 10 milligrams in psoriatic arthritis.

I will now turn the discussion over to Dr. Daniela Graham, who will discuss the safety of tofacitinib in psoriatic arthritis.

Applicant Presentation - Daniela Graham

DR. GRAHAM: Good morning. I'm Dr. Daniela Graham from Pfizer clinical, and I will give an overview of the safety data in the tofacitinib psoriatic arthritis program. The safety of tofacitinib in psoriatic arthritis is consistent with its established profile with no new or unexpected funds. The psoriatic arthritis database is comprised of 783 patients and 775 patient-years of exposure, including data from two pivotal studies and the ongoing long-term extension study

as of May 10, 2016.

The PsA safety data is supported by an extensive base of safety data generated from the rheumatoid arthritis and psoriasis programs, all three totaling approximately 31,000 patient-years of exposure and more than 10,000 patients.

The RA safety database is comprised of approximately 6,300 patients and 22,000 patient-years of exposure. The psoriasis program added an additional 3,600 patients and 8500 patient-years of exposure. In addition, more than 80,000 patient-years of exposure have been accrued in the postmarketing setting.

The PsA safety data were generated in a well-designed comprehensive development program. The safety data are presented in three distinct cohorts, first the 3-month placebo-controlled period, which provides a comparison of all active treatment groups and placebo. This group is particularly useful to examine short-term and routine safety measures such as adverse events, serious adverse events, and adverse events

resulting in discontinuation.

The second cohort describes pooled data from both pivotal study, up to 12 months of exposure for tofacitinib and adalimumab. The tofacitinib treatment arms include data from patients originally randomized to placebo that switched to tofacitinib. The third and last cohort presented includes all data from tofacitinib-treated patients, up to 3 years of exposure in the long-term extension study.

The majority of patients enrolled in the program completed the study they participated in. During the 3-month placebo-controlled period, discontinuations occurred most commonly in the placebo group and were evenly distributed across the active treatment groups.

Including discontinuations due to adverse events, discontinuations due to adverse events were similar between tofacitinib dose groups during the 3-month placebo-controlled period as well as in the 12-month dose comparison cohort.

Discontinuations due to insufficient

clinical response were higher in the placebo group. Patients in the all-PsA cohort will be treated up to 4 years. In this cohort, discontinuations due to any reasons are currently under 10 percent.

In the 3-month placebo-controlled period, the majority of adverse events were reported as non-serious. The frequencies were similar between the active treatment groups and higher than placebo. The most frequently reported adverse events in all treatment groups were nasopharyngitis, upper respiratory tract infection, and headache.

Frequencies of serious adverse events were similar across all treatment groups. The most frequently reported serious adverse events were infections. During the 12-month dose comparison, serious adverse events' frequencies were similar between tofacitinib doses.

Instance rates are presented as patients with events per 100 patient-years of exposure. For data in the up-to-12-month dose comparison, pooled data from the qualifying studies is shown on the

left side of the graph, and corresponding point estimates from study 1091, which was 12 months in duration and included adalimumab, are shown on the right side of the graph.

The rates of serious adverse events are similar between tofacitinib doses and similar to adalimumab within study 1091. As previously noted, infections were the most frequently reported serious adverse event and the most common infection reported, regardless of treatment group, was pneumonia.

There were 4 deaths reported in the PsA program. All patients received tofacitinib. Three of these reported deaths were due to cardiovascular causes in individuals with typical risk factors. There was also one death due to pancreatic cancer. There were no deaths related to study drug based on the investigator's assessment.

The safety profile of tofacitinib in the PsA program was carefully assessed for newly identified or previously identified safety risks. The majority of presentations on these topics are based

on the 12-month dose comparison cohort, as that provides the adalimumab arm for comparison.

For longer latency, low frequency events such as malignancies and cardiovascular events, the all-PsA population is used. Data from the RA and the PsA programs are presented to provide context. To provide contextualization using real-world data, observational data for PsA from the Truven MarketScan Claims database are also presented.

An external comparison cohort was created from this administrative U.S. medical claims database. The cohort is comprised of 5,799 patients with PsA, defined as at least one inpatient or at least two outpatient diagnosis codes of PsA, at least one of them coming from a rheumatologist.

Patients were required to have moderate to severe disease, defined by proxy as treatment with an approved systemic PsA treatment. Exclusion criteria from the tofacitinib global phase 3 PsA studies were also applied to increase comparability with the trial populations.

While this observational comparison cohort serves as an important compliment to the adalimumab active control, comparisons with the phase 3 trial data should be made with consideration of differences in the population characteristics, capture of events, and the limited number of events in the PsA tofacitinib development program.

Serious infections were defined as infections that required in-hospital treatment and/or parenteral antimicrobials. There were 7 serious infections reported in the up-to-12-months cohort in the PsA program, and the incidence rate ranged between 1 and 2 for both tofacitinib doses and adalimumab. All serious infections reported resolved after treatment.

Comparisons of the incidence rates between the PsA, the RA, and the PsO programs, and the Truven cohort are shown next. To the left of the dotted line are the incidence rates corresponding to clinical trial data in each tofacitinib development program. On the far right is the incidence rate from the Truven observational

cohort.

The incidence rates of serious infections were consistent regardless of the patient population treated with tofacitinib and consistent with the Truven cohort. This is generally consistent across infection type with the exception that an increased risk of herpes zoster has been associated with tofacitinib compared to TNFi's.

In the PsA studies, all reported cases of herpes zoster were observed in tofacitinib-treated patients. The incidence rate of herpes zoster was approximately 1.5 to 2 per 100 patient-years of exposure. When this rate is compared to the Truven cohort and data from the RA and the PsO tofacitinib programs, the point estimates are in the range of 1 to 3 events per hundred patient-years for tofacitinib in the three development programs. This is similar to the incidence rates observed in the Truven cohort.

We are now going to discuss the longer latency and low frequency events such as malignancies and cardiovascular events. Due to the

low number of events, the all-PsA cohort is used for these presentations.

Major adverse cardiovascular events is a composite cardiovascular endpoint frequently used to assess cardiovascular risk in clinical trials. MACE events reported during the PsA program in tofacitinib-treated patients were sudden cardiac death, as presented before, non-fatal myocardial infarction, and non-fatal ischemic stroke. An additional ischemic stroke was reported in a patient treated with adalimumab.

When the rates of MACE are compared between the PsA, the RA, and the PsO tofacitinib programs, and the Truven cohort, the incidence rates are similar.

Incidence rates were also evaluated over time at 6-month intervals for each tofacitinib development program. The PsA data is shown in green, the PsO data is shown in yellow, and the RA data is shown in blue. The rates for MACE in the PsA program do not tend to increase over time and are within the range of dose observed in the other

development programs where they have remained stable.

The discussion of malignancies will start with malignancies excluding non-melanoma skin cancers followed by a discussion of non-melanoma skin cancers. There were 5 malignancies reported; 4 of the 5 malignancies occurred within 3 months of starting tofacitinib; 2 of them, the renal and pancreatic cancers, followed 12 months of treatment with adalimumab in the pivotal study.

When the rates of malignancies are compared between the PsA, the RA, and the PsO tofacitinib program and the Truven cohort, the incidence rates are similar, though the confidence interval in the PsA data is wide.

When observed in 6-month intervals over time, the incidence rates of malignancies in the PsA program are within the range of those observed in the other tofacitinib development programs, where they have remained stable.

Four non-melanoma skin cancers were reported in individuals with typical risk factors. These

tumors were non-invasive and result after usual treatment. When the rates of non-melanoma skin cancer are compared between the PsA, the RA, and the PsO tofacitinib programs and the Truven cohort, the incidence rates in the PsA program are similar to those observed in the RA and PsO programs. The rate for the Truven cohort is 1.4. There were no cases of melanoma reported in the PsA program.

To conclude this session, the remaining events of special interest are presented. Laboratory changes observed in the PsA program showed similar trends to those observed in the RA and the PsO programs. These include modest dose-dependent decreases in hemoglobin, neutrophils, and lymphocytes.

Decreases in lymphocytes were not seen in the short-exposure cohorts, but were observed in the long-exposure cohorts. Modest dose-dependent increases were observed in LDL and HDL, and modest dose-dependent increases were observed in liver enzymes and creatinine. There was one event of an appendicitis with perforation, no events of

interstitial lung disease and/or tuberculosis, and no significant hepatic events.

In conclusion, the safety profile of tofacitinib is well characterized, stable, and manageable. It is informed by a large and growing safety database with consistency between the real world and clinical safety data.

No new signals have been identified in the PsA program. The rates of adverse events of special interest are similar to those observed in biologics DMARDs with the exception of herpes zoster and are consistent with the RA and PsO safety databases.

I will now hand over to Dr. Thomas Jones, who will describe the risk management strategy to address these risks.

Applicant Presentation - Thomas Jones

DR. JONES: Thank you, Dr. Graham.

I'm Thomas Jones, the safety risk lead in the psoriatic arthritis program. Risk management for tofacitinib is ongoing. I will summarize this approach, which has been and continues to be

effective in RA, and convey how we rely substantially on this experience in RA as we plan for risk management in PsA.

One arm of the approach is risk mitigation. When tofacitinib was approved in 2012 for RA, risk mitigation involved not only the product labeling, but also a targeted plan to communicate important risk information to healthcare professionals.

In 2016, Pfizer was released from this risk evaluation and mitigation strategy, or REMS program, based on findings from survey-based assessments that showed that the risk mitigation measures were working well.

Risk mitigation now is focused on the product labeling. The other arm of risk management that I will be speaking about is pharmacovigilance, which encompasses both risk assessment and reporting. Given the consistency between the safety profile and tofacitinib in PsA and in RA, the proposed risk management approach in PsA build substantially on the effective approach in RA.

All of the adverse drug reactions that are

associated with tofacitinib were identified based on the review of data from clinical studies in the RA program. No additional adverse drug reactions have been identified from the review of four and a half years of postmarketing data with more than 80,000 patient-years of exposure.

Notably, there are no new risks for tofacitinib identified in the PsA program. So the same risks and additional safety information shown on the left side of the slide are addressed by the same risk mitigation via the product labeling.

The product labeling includes information in several sections, including the boxed warning, the warnings and precautions section, the dosage administration section, and in some cases the patient counseling section and the medication guide, which in totality provides information for the prescriber on considerations before initiating therapy and during therapy and, where appropriate, guidance on dose modifications, monitoring, and other safety risk-related guidance.

Pharmacovigilance for tofacitinib

encompasses both risk assessment and reporting. Assessment consists of routine monitoring for changes in all the identified risks, potential risks, and other safety information that's shown, and detection of new signals.

Notably, since tofacitinib was approved for the treatment of RA in 2012, more than 20 safety signals have been opened and evaluated. For example, a signal of non-melanoma skin cancer was opened, and after thorough evaluation, it was determined that there was sufficient evidence that treatment with tofacitinib was causally related to non-melanoma skin cancer.

A labeling change was made to identify non-melanoma skin cancer as an adverse drug reaction, with text recommending periodic skin exams in patients at increased risk for skin cancer. Conversely, for a signal of deep vein thrombosis and pulmonary embolism, the signal was closed when it was determined that there was no evidence of dose dependency and there were no differences between the tofacitinib frequencies and the

background risk in rheumatoid arthritis patients.

For a signal of pancreatic cancer, the signal was closed when it was determined that there was no evidence of biologic plausibility, noting especially the very short time interval between the exposure to tofacitinib and the diagnosis of pancreatic cancer in the patients.

When signals are closed, they can be reopened if evidence from ongoing pharmacovigilance warrants doing so. Reporting is accomplished by sending periodic aggregate safety reports to regulatory authorities and by sending individual case safety reports to investigators and independent ethics committees in association with ongoing clinical studies. This same approach to assessment and reporting is proposed for PsA.

In addition to routine monitoring and reporting, pharmacovigilance and PsA will include analysis from findings from the ongoing open-label long-term extension study, A3921092.

An additional activity will be to extend the ongoing organization and teratology information

specialist, or OTIS, pregnancy registry in RA patients to include PsA, to monitor the effects of tofacitinib on pregnancy and on the fetus.

Further, given the consistency of the safety profiles in PsA and RA, the safety profile on PsA will be further informed indirectly by the findings from two other pharmacovigilance activities that are ongoing for RA.

One is a long-term prospective non-interventional comparative safety study embedded within the Corrona registry, comparing rates of malignancy, cardiovascular events, serious infections, and other safety outcomes among patients treated for moderately to severely active RA. The other is a large long-term post-approval clinical safety trial, study A3921133, which I'll describe in more detail.

This randomized open-label blinded endpoint study is an event-driven clinical trial of more than 4,000 moderate to severe RA patients who have cardiovascular risk factors. An important milestone was achieved earlier this year when the

first visit occurred for the last subject to be recruited and enrolled. Read-out of the study data is anticipated in 2020.

The primary focus is evaluating the safety of 2 doses of tofacitinib versus a TNF inhibitor. The co-primary endpoints are major adverse cardiovascular events and malignancies. And the secondary objective is to evaluate opportunistic infections, serious infections, and other safety risks.

The study includes both an external steering committee and an external data safety monitoring board, and several of the endpoints were adjudicated by blinded external committees.

Risk management for tofacitinib in RA, including both risk mitigation through the product labeling and robust pharmacovigilance, has been and continues to be effective, and the proposed approach to risk management of PsA will build on that approach and on the consistency between the safety profiles for PsA and RA.

Pfizer's warnings from pharmacovigilance

activities enhance the characterization of the safety profile and further inform on the adequacy of risk mitigation measures, which in turn helps to maximize the favorability of the benefit-risk profile.

Noting this critical role of risk management in the benefit-risk assessment, I'd like to turn the presentation over now to Dr. Michael Corbo for an overview of the benefit-risk of tofacitinib in psoriatic arthritis.

Applicant Presentation - Michael Corbo

DR. CORBO: Throughout this morning, we together with the FDA will have reviewed the efficacy and safety of tofacitinib in the treatment of psoriatic arthritis.

As discussed by Dr. Mease, psoriatic arthritis is a distinct complex disease with multiple manifestations encompassing peripheral joints, tendons, ligaments, bone, and skin. Also, Dr. Mease noted that substantial unmet need remains, with many patients unable to function in the normal course of their lives, leading patients

and physicians to seek alternative therapies to treat this disease.

We will assess the benefits and risks of tofacitinib at a dose of 5 milligrams twice daily in the treatment of patients with psoriatic arthritis, which is our intended label dose. The format of this discussion will be to discuss the benefits, the risks, and risk mitigation with context for each topic. We will then conclude with benefit-risk.

With respect to the benefits, tofacitinib at a dose of 5 milligrams met the primary endpoints in both pivotal studies as measured by the ACR20 response and the response in the change in HAQ-DI. Importantly, improvements in these primary endpoints were noted at 2 weeks, which was the first assessment in these studies.

When looking at the collective efficacy data, including the prespecified pooled data set, tofacitinib demonstrated consistent and clinically meaningful improvement across multiple manifestations of psoriatic arthritis, including

peripheral arthritis at the higher order, ACR50 and 70, the resolution of enthesitis, the resolution of dactylitis, and psoriasis response, as measured by the PASI75.

This supplemental program was not designed to definitively demonstrate inhibition of structural damage in PsA. Rather, the goal of adding x-rays was to ensure that patients on tofacitinib did not silently progress while improving in signs and symptoms. That being said, we did note a similar lack of progression in the tofacitinib-treated patients as those treated with adalimumab after one year of treatment.

Given the precedented mechanism of action of tofacitinib, and the inhibition of structural damage in rheumatoid arthritis, and the proportion of patients with erosive disease at baseline, it's likely that some patients would have progressed to a detectible level had they not been effectively treated. While these data are certainly not definitive, they do provide useful information for healthcare professionals.

In addition to treating patients' disease and these manifestations of PsA, we also seek to improve the quality of life of patients. We have investigated a suite of patient-reported outcomes, as you've seen in Dr. Kanik's presentation, including physical function, health-related quality of life, and fatigue.

Clinically meaningful improvements were observed across the entire range of patient-reported outcomes in both the biologic-naive and anti-TNF inadequate responder patients. These results were consistent when looking at the population data, as shown in Dr. Kanik's presentation, or patient-level data with a proportion of patients achieving an MCID, as shown here.

These data are important, and together with the core efficacy data, demonstrates substantial benefit in the treatment of psoriatic arthritis of tofacitinib at 5 milligrams.

In any assessment such as this, it's important to place context around the data whenever

possible. In the PsA program, we did include an active comparator in our biologic-naive study, which can provide some context as to the benefit in psoriatic arthritis.

In navigating this context assessment, the green portion of the graph represents data favoring tofacitinib over adalimumab. For some measures, a higher score is better, as you'll see on the left, and for others, a reduction in score is better, as you see on the right.

Tofacitinib delivered similar benefit relative to adalimumab across multiple disease manifestations of psoriatic arthritis in this biologic-naive population. Additionally, tofacitinib delivered consistent results even in anti-TNF inadequate responder patients. This indicates that tofacitinib at 5 milligrams delivers substantial benefit.

With respect to the risks associated with tofacitinib therapy, we are fortunate to have a long and thorough foundation of knowledge when it comes to their assessment. As you have heard, we

have a cumulative knowledge of safety of exposure of tofacitinib, encompassing over 30,000 patient-years in clinical trials in RA and psoriasis with exposure durations of up to 9 years in patients with RA and approximately 80,000 patient-years of real-world data.

Our psoriatic arthritis program was designed and sized to support a supplemental application, leveraging our existing development experience. Given the similarity and the risk profiles between psoriatic arthritis and rheumatoid arthritis in the literature and a consistent safety profile of tofacitinib between PsA, RA, and psoriasis, we can look at the PsA safety data in the context of the RA and psoriasis safety experience.

As discussed by both Drs. Graham and Jones, there have been no new risks identified in the PsA program. With respect to infections, based upon our clinical trial experience, infections present in a typical manner, respond to treatment, and follow a typical course.

Lab changes are well documented, and there

are labeling recommendations already in place for these. Non-melanoma skin cancer is an identified risk that is managed through labeling with periodic skin exams recommended. These events have been non-complicated and have been effectively treated with usual methods.

As with any immune-modulatory therapy, malignancies are a potential risk, and we have been evaluating MACE throughout our entire clinical program as well as our postmarketing commitments.

To place these risk data into context, already in Dr. Graham's presentation, you have seen that we've looked at the relative risk to adalimumab. We can now also look at the broader safety experience of tofacitinib in psoriatic arthritis, rheumatoid arthritis, and psoriasis.

As we look across all three of our phase 3 experiences with tofacitinib, we can see consistency in the risk profile across these diseases. As examples, we're displaying data from short-term events such as serious infections here to long-term latency effects such as malignancies

and MACE. This provides context that the risks associated with tofacitinib therapy have been consistent across these three diseases.

While we understand these risks quite well, it's important to manage them. As the risks of tofacitinib treatment are highly consistent between PsA and RA, the risks should effectively be managed with the core risk management in place for rheumatoid arthritis.

In addition, as Dr. Jones noted, we will have some specific psoriatic arthritis additions to the risk management program. To provide context for the risk management approach, we have observed similar incidence rates of serious infections between our clinical trial experience and real-world reporting from the Corrona registry. These data suggest that the current risk mitigation approaches such as those utilized in the RA label are effective and well understood by healthcare professionals.

There are multiple means of assessing benefit-risk, including quantitative and

qualitative approaches. Number needed to treat and number needed to harm represents the additional number of patients needed to achieve a defined measure of benefit or a defined adverse event. One looks to have a small number needed to treat and a large number needed to harm.

We examined a group of benefits and risks based upon physician and patient prioritization. Looking across the ACR50, the resolution of enthesitis and dactylitis, and the FACIT response in measuring fatigue at 3 months, we can see in general that the numbers needed to treat are within the single digits, while number needed to harm based upon the broader tofacitinib experience at 3 months for serious infections and herpes zoster were between 100 and 500.

In assessing the qualitative benefit-risk of tofacitinib in the treatment of psoriatic arthritis, there are several key medical needs when considering the treatment of PsA. First, as Dr. Mease discussed, this is a complex disease with multiple manifestations. Tofacitinib demonstrated

activity across these key disease manifestations, in patient populations ranging from biologic naives through anti-TNF failures, with an onset of efficacy as early as 2 weeks.

Additionally, tofacitinib offers an alternative mechanism of action for the treatment of PsA, and being a small molecule, offers oral administration without the concerns of anti-drug antibody development. Also, tofacitinib demonstrated improvement in quality of life at both the population and the patient level.

The risks with tofacitinib therapy are well understood, including infection such as herpes zoster, non-melanoma skin cancer, and the potential risk of other malignancies. Once again, these are consistent with the RA risk profile for which we have an effective risk management plan in place.

Based upon the overall efficacy profile in this complex disease and the well understood risk profile of tofacitinib, we have demonstrated that the overall benefit-risk of tofacitinib at 5 milligrams twice daily is favorable in psoriatic

arthritis patients.

In conclusion, at Pfizer, we are committed to the safe and effective use of our products. We have demonstrated this commitment in the clinical development and the postmarketing assessment of tofacitinib in rheumatoid arthritis, and we will continue this commitment in psoriatic arthritis. Most importantly, we are committed to patients living with psoriatic arthritis and hope to bring a new therapeutic option to them.

On behalf of our entire team here today, we would thank the committee and the FDA for your thoughtful attention and assessment as we share a common objective in doing the right thing for psoriatic arthritis patients. We look forward to answering your questions.

Clarifying Questions

DR. SOLOMON: Thank you very much. We now have time for some clarifying questions. Let's start it off with Maria.

DR. SUAREZ-ALMAZOR: Yes. Suarez-Almazor. Thank you for your presentation. I have some

questions related to the MarketScan data. You were using that to base some of your conclusions on safety.

MarketScan data is based on claims. So how did you ensure that the identified events were actually incident case? Because if you're just using claims over a one-year period of time, you may be including a claim that's just reflecting a prevalent disease, and that would inflate the number of events in the control that you're using.

Furthermore, for malignancies, the MarketScan data is not linked to registry, cancer registries, so you could have misclassification in cases that are just based on a claim. So all of that would increase the rate of events in your controls.

DR. KANIK: Thank you. I would like to invite Dr. Niki Palmetto to the lectern to discuss the Truven market analysis.

DR. PALMETTO: Niki Palmetto, Pfizer epidemiology. The external comparison cohort was constructed to reflect the clinical trial

population as closely as possible within an observational setting, namely by requiring systemic PsA treatment to proxy moderate to severe disease, applying clinical exclusion criteria, and defining the outcomes similarly across the two databases.

While this data provides an important complement to the internal comparator data, a comparison should be made with consideration of the inherent differences between the two data sources as you note.

To determine the incident cases of the safety events, we used the year prior and all available follow-up time prior to the index date. And as you note, there are some limitations in that because events could have occurred prior, but we estimated the number of new events occurring on the new treatment, so a new use of a treatment. So for all available data, we know that there's a new event per the new use.

DR. SUAREZ-ALMAZOR: So new means no prior event with the same claim for 12 months before entering the cohort?

DR. PALMETTO: Yes. For the specific biologic, yes.

DR. SUAREZ-ALMAZOR: Thank you.

DR. PALMETTO: In regards to your non-melanoma, can you repeat your question again? It was about the capture of that.

DR. SUAREZ-ALMAZOR: Yes. For the malignancies, I was wondering because I know that the data is not linked to registry data, so you don't have a histologic diagnosis; it's just on the basis of a claim. So someone says this patient had colon cancer and you put that on the claim, but they may not have colon cancer first.

DR. PALMETTO: Yes. You are exactly right. These are based on IC-9 codes for claims purposes. We did use validated algorithms that were previously validated in an EHR or claims database, and the algorithm includes a diagnosis code plus some evidence of treatment, such as biopsy, pathology, et cetera. So it's not simply the diagnosis codes. It's also evidence of treatment.

DR. SOLOMON: Michael?

DR. WEISMAN: Question about the rationale for using the higher dose in your clinical trials. Can you explain that a little bit? What did you expect to see with the 20-milligram total dose? And is it related at all to your view of psoriatic arthritis? The higher dose is sometimes used with the TNF drugs.

Please give us a sense of the purpose of the higher doses and what the findings were that differentiated the higher dose and the lower dose.

DR. KANIK: We chose the doses for the phase 3 program based upon the dose ranges for rheumatoid arthritis and psoriasis. And in their phase 3 programs, they saw more of a dose effect, particularly I think in the psoriasis program, between 5 and 10.

Since we did not do any phase 2 dose ranging, we did not know whether 10 milligrams would be needed for the additional manifestations like enthesitis or dactylitis and for psoriasis. What we found in our program was that 10 was not providing any much more added efficacy relative to

the 5 milligrams.

You can see most similarities between 5 and 10 on the arthritis endpoints, the studies were powered for arthritis. On the enthesitis and dactylitis, you can see a little bit more variability. But overall, there's very little difference between 5 and 10 on efficacy. And for that reason, we didn't feel the need to propose 10 milligrams going forward for PsA.

DR. WEISMAN: I did notice that, at least in enthesitis, the 10-milligram dose did better. Is that right? Was it statistically better than the 5 dose or does it just look better?

DR. KANIK: It depends upon the study. Let me have MA-49, please. In the TNF-naive study, at 3 months, 10 milligrams was statistically significant. However, by month 6, the next time point evaluated, 5 and 10 were very similar.

In the TNFi-IR study, which should be a more recalcitrant patient population, there were very few differences between 5 and 10 overall over the course of the study. If you actually pool those

two studies together, you find that the 5 and 10 are fairly similar.

DR. WEISMAN: But were they different from each other at 3 months?

DR. KANIK: In the TNFi-naive study, 1091, yes. One was statistically significant; the other one was not.

DR. SOLOMON: Beth?

DR. JONAS: Thank you for your presentation. My question is related to background conventional DMARDs. If I was reading the briefing material, I think on page 37, it looks like between 75 and 80 percent of patients remained on methotrexate during the course of this study.

Is that correct? Am I reading that right?

DR. KANIK: Yes. Around 82 percent of patients remained on methotrexate, and the rest were on other conventional DMARDs such as leflunomide and sulfasalazine.

DR. JONAS: So do you have any data on the dose of methotrexate in patients in the studies? And were there any differences between patients who

were on concomitant methotrexate versus patients who received monotherapy with tofa or adalimumab?

DR. KANIK: There was no monotherapy with tofacitinib in these studies. The studies required as part of the protocol inclusion/exclusion criteria they had to be on a background CS DMARD, so we do not have any monotherapy data.

We have done subpopulation analysis on the ACR20 and HAQ-DI, showing that there were no differences between those patients who were on methotrexate and those patients who were on other commensurate synthetic DMARDs.

In regards to the baseline methotrexate dose, if I can have slide EF-115 up, please. The maximum dose of methotrexate that was allowed in those days was 20 milligrams. Our doses in general were a median of 15 milligrams, which is consistent with the practice. There was no specific dose that was required. They just had to be on methotrexate, though.

DR. JONAS: Thank you.

DR. KANIK: Slide down, please.

DR. SOLOMON: I have a couple questions. Slide 67 showed some information on deaths, and maybe I just wanted to see that again and maybe review it. It seems like there were only deaths in the tofa arm. Is that true?

DR. KANIK: That is correct, and I'd like to invite Dr. Daniela Graham to the lectern to discuss the deaths in the psoriatic arthritis program.

DR. GRAHAM: Daniela Graham, Pfizer clinical. If I could have MA-67 up, please? There were 4 deaths in the PsA program. As you can see in the slide, these 4 patients were receiving tofacitinib. There was no deaths during the placebo-controlled period. Two of the patients that were initially randomized to placebo had already advanced to tofacitinib at the time of the event.

DR. SOLOMON: Another safety question that I had was MA-73, which was on herpes zoster. If you could bring that slide up.

DR. KANIK: Could I have MA-73 up, please?

DR. SOLOMON: So what struck me was looking

at the Truven rates for any biologic DMARD at 1.26, I wanted to see the tofa data on the left. I was surprised that you hadn't tried to group those data together. It seemed like that would have been the obvious way to analyze these data, to have a much narrower confidence interval, and we can see whether it was really a difference. Or was the assumption just that we know that shingles is higher, so why analyze the data that way?

DR. KANIK: I would like to invite Dr. Hernan Valdez to the lectern to discuss the overall rates of zoster in the tofacitinib programs.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. In the more extensive rheumatoid arthritis development program, we found that the use of corticosteroids and age were associated with an increased risk of herpes zoster. And due to that heterogeneity in age and the proportion of use of corticosteroids, we thought it most appropriate to present the incidence rates for each indication.

In the psoriasis development program,

patients were on tofacitinib monotherapy alone. In the rheumatoid arthritis development program, 80 percent of patients use corticosteroids, and only 20 percent of the patients used corticosteroids in the PsA development program.

DR. SOLOMON: Just to see the slide again please. So in the PsA program, the incidence rate was about 2 versus 1.25 versus other biologic DMARDs for PsA. Am I reading that correctly?

DR. KANIK: That is correct

DR. SOLOMON: I understand there is wide confidence intervals, but the data that we're being shown suggests a higher rate, even in a population that receives little amount of corticosteroids.

DR. KANIK: That is correct. Increased herpes zoster has been seen with tofacitinib treatment, and we see it in both the psoriasis, rheumatoid arthritis and psoriatic arthritis development programs.

DR. SOLOMON: I'm just going to follow up on this line, and then I'll pass on. So just to go to the pharmacovigilance issue because this seems to

me a critical issue in pharmacovigilance, is how we're managing the shingles risk.

I wasn't quite clear on how the risk mitigation strategy has dealt with shingles. There was discussion that a survey had suggested that the risk mitigation was working, but there is no data shown from the survey, so I'm not really quite sure what you're talking about.

DR. KANIK: Thanks. Yes. Our risk mitigation program has evaluated that, and I'd like to have Dr. Thomas Jones come to the lectern to discuss the risk mitigation program and zoster evaluation.

DR. JONES: Thomas Jones, safety risk lead, Pfizer. In speaking about the risk mitigation in the labeling, there is a statement that recommends that patients be brought up to date with all the appropriate vaccinations that are recommended for that patient based on age, for example, so that general recommendation of updating their vaccinations.

We do not have any data that looks

specifically at whether or not that is producing a difference in, for example, the frequency of patients in the postmarketing data that are experiencing herpes zoster. There's been no significant change over time in reflecting an increased risk, but we don't have any way of directly determining rates in the postmarketing data to really assess whether there's been a drop in rates over time, either.

DR. SOLOMON: I actually don't understand that last statement. There's no way to assess a change in rate?

DR. JONES: The rates that we would estimate in postmarketing data would be really just estimates based on what we believe is the exposure, but that's a calculation of exposure based on a variety of sources. But it's not a precise estimate of exposure, so it's difficult to ascertain a precise rate.

DR. SOLOMON: A rate of vaccination or a rate of shingles?

DR. JONES: A rate of shingles.

DR. SOLOMON: But you have shown us a lot of claims data, and I'm just trying to understand how to put all these data together regarding safety. You're showing us claims data, which would have information about vaccination rates and shingles, but you're saying there's no way to get these other rates.

DR. JONES: There were numbers shown for total experience in that data, but no -- we do not have data looking, for example, at time-based analysis of the change in rate over time, during the period at which tofacitinib for rheumatoid arthritis has been approved.

DR. SOLOMON: Other questions? Alyce said no. Diane?

DR. KANIK: If the committee chair would allow, I'd like to bring up another member, one of my colleagues, to discuss this issue.

DR. SOLOMON: Please.

DR. KANIK: I would like to bring up Dr. Hernan Valdez to the lectern, and after him, I'll bring up Dr. Kevin Winthrop.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. Although we have not prospectively studied the rate of vaccination in patients with hematologic diseases, we have some evidence that suggests that rate of vaccination is increasing.

During the inception of the tofacitinib development program, the rate of vaccination in the patient's medical history was less than 5 percent, and Dr. Winthrop has investigated that in a much larger population.

More recently, we conducted a study, A3921187, that had a substudy of immunization with a current live vaccine, Zostavax, and the proportion of patients that had already been vaccinated was actually 20 percent. So there is some circumstantial evidence suggesting that the rate is going up.

We are further committed to investigating and trying to prevent the risk of herpes zoster. So if the new subcomponent adjuvant vaccine that's being developed is approved, we have already in the plans to conduct a clinical study to actually

demonstrate a decrease in the clinical cases of herpes zoster.

DR. WINTHROP: I'm Kevin Winthrop, and I'm from Portland, Oregon and Oregon Health and Science University. I should disclose that I've been a paid scientific consultant. I've received grant funds from both Pfizer and other companies who are developing JAK inhibitors. So I've done quite a bit of research as a researcher and consultant on a number of these products.

Just to get some context in, Dr. Solomon, I appreciate your questions. I had many of the same questions. In terms of real-world data, Jeff Curtis and I did publish a study recently where we looked at the rate of herpes zoster with tofacitinib in U.S. claims data. And this was an RA population, where there's enough of that data to look at.

Actually, what we found when we reviewed the development program data in RA is that the rate of herpes zoster is about 2-fold higher in patients using tofa as compared to RA patients using other

biologics.

This Truven comparison, I think it was a good study. I was also involved in that as well. But lower rates were found, and there's probably reasons for that that were alluded to by Dr. Valdez in terms of steroids and age structure, those cohorts.

In terms of vaccination, I can just tell you what I do personally. I recommend patients going on any JAK inhibitor to get vaccinated before they go on it if they meet the age criteria for the vaccine. And that's also true of any biologic. I mean, as you note, the current vaccine is a life vaccine.

So the window to vaccinate anyone is before they go on any biologic or JAK inhibitor. So it's really the time you've got to do it. So I think, if anyone is switching therapies or starting a therapy, it's the right time to do it. So I think it's a good consideration.

I have the same interest in the studies I think you're bringing up. I mean, I'd like to know

what the uptick in vaccination has been. Jeff Curtis and I have done a lot of work on this issue. We published a paper a few years ago that the prevalence of vaccination in RA was pretty low at that time. That study is four or five years old, so it's probably time to go back and measure that again. Thanks.

DR. SOLOMON: Thanks. Diane Aronson?

MS. ARONSON: I guess, in the psoriatic arthritis cohort 3, 2 patients developed or reported an adverse event of increased creatinine by acute renal failure. One patient was in a setting of dehydration, hypotension.

I understand the limited number here, but I did a quick social check and patients are talking about blood, nausea, and vomiting.

So in recognition of dehydration, can you tell me what the mitigation is or how patients take this, just so I know? Are they taking it with or without food or can you just comment on that, please?

DR. KANIK: Tofacitinib can be taken with or

without food. I would like to invite Dr. Thomas Jones to the lectern to further discuss this.

DR. JONES: Thomas Jones, safety risk lead, Pfizer. In the product labeling, there are no stipulations in terms of restrictions of how it's taken in relationship to meals or in terms of hydration.

Certainly, just in the context of general discussions between the prescriber and the patient, hopefully it's understood that there would be conversations about appropriate ways to use the drug in terms of how to take it, but there's nothing else further stipulated in the product labeling.

DR. SOLOMON: Erica Brittain?

DR. BRITTAIN: Since there was no placebo comparison possible for the radiographic endpoint, it might have been natural to set up a non-inferiority comparison with the active control drug. You discuss this a bit, but I just wondered if you could provide more perspective about why you opted not to do that.

DR. KANIK: We chose not to compare versus placebo because we chose not to have a study that caused irreversible progression in patients who are on placebo. Since we had adalimumab and we planned this to be a reference-arm study, we wanted to have a comparison with adalimumab, but we did not really have a good idea of how to design a non-inferiority study in a phase 3 study looking at radiographs.

I'd actually like to bring up Dr. Stan Cohen to the lectern to discuss this further.

DR. COHEN: Good morning. I'm Stanley Cohen. I'm a rheumatologist from Dallas, and I'm an external consultant to the sponsor. But I think we're going to have a whole discussion about this when Dr. Nair presents his data.

I think at the time, that wasn't really something that was -- how to determine the non-inferiority margins was not clear at that point, still not totally clear, but there's some hope that we can move forward as we get away from placebo-controlled trials and look at radiographic outcomes where you see a change in a modified Sharp score of

0.5 or 1 over 6 to 12 months.

So as we move to active comparator studies, I'm real intrigued by the presentation we'll hear next, and hopefully this will be a roadmap that we can move forward and do more active comparator studies looking at radiographic outcomes.

DR. SOLOMON: Could I just follow that up? I wasn't actually sure what the hypothesis of those comparisons were. Was it non-inferiority? Was it a formal non-inferiority? Was it superiority or was it just purely descriptive?

DR. KANIK: It was purely descriptive. We wanted to estimate and compare the treatment effects of adalimumab and tofacitinib at 12 months on radiographs, but we did not have any formal non-inferiority testing with adalimumab, nor superiority versus placebo.

DR. SOLOMON: So the obvious question is, what inferences should we draw?

DR. KANIK: I think what we can draw from this is that in a patient population, that a majority had elevated C-reactive protein and most

had pre-existing structure damage that should have progressed. There was no progression seen in any of the tofacitinib -- or little, practically none, progression seen in either tofacitinib 5, 10, or adalimumab.

The initial reason for doing these radiographs, based upon advice we got from both the U.S. and European regulatory agencies, was that in patients who were improving with signs and symptoms on tofacitinib, were we seeing after 12 months in therapy changes in progression. And we did not. We saw that they were similar to adalimumab, which we know and has established efficacy in structured damage in patients with psoriatic arthritis.

DR. SOLOMON: Thanks.

Any other points people want to raise, clarifying questions before we move on?

(No response.)

DR. SOLOMON: Seeing none, we will now proceed with the FDA presentations.

FDA Presentation - Raj Nair

DR. NAIR: Good morning. My name is Raj

Nair, a medical officer in the Division of Pulmonary, Allergy, and Rheumatology, and I am a practicing rheumatologist. Today, we will discuss tofacitinib for use in psoriatic arthritis.

The studies provided by the applicant to support the use of tofacitinib in psoriatic arthritis use the immediate-release formulation. I will be presenting data using the immediate-release formulation of tofacitinib, which has been bridged to the extended-release formulation.

I will start with an introduction and clinical overview, Dr. Rothwell will present statistical considerations on efficacy, then I will provide a safety summary and end with risk-benefit considerations.

Tofacitinib is a JAK inhibitor approved in the United States for use in rheumatoid arthritis since 2012. Five milligrams orally twice daily is approved for the treatment of rheumatoid arthritis. The applicant submitted a supplemental new drug application proposing to use tofacitinib in active psoriatic arthritis. The proposed dosing for

psoriatic arthritis is 5 milligrams orally, twice daily, used in combination with conventional synthetic DMARDs.

The following are key interactions between the applicant and the agency. The applicant's initial psoriatic arthritis trial proposed a 6-month placebo period to compare with tofacitinib. The agency was concerned that the patient population proposed was at high risk for uncontrolled disease activity and irreversible radiographic progression.

The agency was concerned that there were several FDA-approved therapies approved to inhibit radiographic progression in psoriatic arthritis. The agency asked that the protocol be modified so that patients were on background DMARDs.

The applicant proposed studies 1091 and 1125 in which all patients received at least one background DMARD and all patients randomized to placebo were advanced to tofacitinib at month 3.

The clinical development program for tofacitinib in psoriatic arthritis consisted of the

studies shown. I will highlight the populations studied in the psoriatic arthritis studies, and Dr. Rothwell will provide further details on the study design during her presentation.

Study 1091 was one of two randomized placebo-controlled studies in psoriatic arthritis patients. The study also included a comparison to adalimumab. The patients recruited to the study were patients who had inadequate response to DMARDs and were naive to TNF inhibitors. Study 1125 was in a population of patients who had inadequate response to TNF inhibitors.

In both studies, patients in placebo treatment arms were switched to 5 milligrams twice daily or 10 milligrams twice a day of tofacitinib after 3 months on placebo. Patients at 6 months from study 1125 and 12 months from study 1091 were eligible to continue an open-label extension study, 1092. In the extension study, patients were placed on 5 milligrams twice a day of tofacitinib, but were allowed to adjust dose as necessary between the 5-milligram and 10-milligram doses.

I have completed the introduction and clinical overview portion of the presentation. Dr. Rothwell will now present the statistical considerations on efficacy portion of the FDA presentation.

FDA Presentation – Rebecca Rothwell

DR. ROTHWELL: Good morning. My name is Rebecca Rothwell. I am a statistical reviewer from the Office of Biostatistics, and today I will discuss the clinical efficacy findings from this submission.

In this presentation, I will begin with an overview of the efficacy evaluation, including a brief review of the study designs. I will then discuss the key efficacy results from the primary and secondary endpoints, including the effect of tofacitinib on the signs and symptoms and physical function of patients with psoriatic arthritis.

I will also discuss the evidence for effect on prevention of joint damage progression as measured by radiographs. I will end with our conclusions about the efficacy of tofacitinib in

the treatment of psoriatic arthritis.

The efficacy evaluation was based on two phase 3 multi-center randomized parallel-group double-blind placebo-controlled studies. In each study, there were two primary endpoints. The first of these was the proportion of subjects achieving ACR20, defined by the American College of Rheumatology as greater than 20 percent improvement in signs and symptoms.

The second primary endpoint was the change from baseline in the Health Assessment Questionnaire Disability Index Score at month 3. Secondary endpoints in each study included assessments of enthesitis, dactylitis, and quality of life. One study evaluated the prevention of radiographic progression.

Before discussing the efficacy results, I would like to review the study designs for study 1091 and study 1125. Study 1091 had a 12-month double-blind treatment period. A total of 422 subjects were randomized to 5 sequence arms.

On sequence A, subjects received tofacitinib

5 milligrams twice daily. On sequence B, subjects received tofacitinib, 10 milligrams twice daily. On sequence C, subjects received the active comparator, adalimumab, at the approved dose of 40 milligrams subcutaneously, administered every other week.

Sequence D received placebo for the first three months of the study and received tofacitinib, 5 milligrams twice daily for months 4 through 12. Similarly, sequence E received placebo for the first 3 months of the study, and then received tofacitinib 10 milligrams twice daily for months 4 through 12.

The primary endpoints were evaluated at month 3. From study baseline through month 3, subjects on sequences D and E received only placebo. Therefore, month 3 comparisons against placebo were made using this combined placebo arm.

The study design for study 1125 was very similar to study 1091, however, there were only 4 treatment arms, eliminating the active control, adalimumab. This study also was shorter in

duration with a double-blind treatment period of 6 months.

As in study 1091, subjects in sequences C and D both received placebo only through month 3, and this combined arm was used for placebo comparisons.

I will now discuss the key efficacy results presented in this application. The first primary endpoint in each study was the proportion of subjects with an ACR20 response at month 3. The prespecified analysis for this endpoint and all other binary endpoints was a normal approximation for the difference in binomial proportions. Subjects with missing data were treated as non-responders.

As shown in this slide, tofacitinib treatment was associated with a higher proportion of ACR responders in both trials at both the 5-milligram and 10-milligram BID doses, and the difference was statistically significant compared to placebo.

Neither superiority nor non-inferiority

comparisons between tofacitinib and adalimumab were key objectives of this study. Responses with respect to symptoms and function were generally similar between tofacitinib 5 milligrams and adalimumab.

In the comparison of the applicant's proposed dose of 5 milligrams versus placebo, there is approximately a 17 percent absolute difference in response in study 1091 and 26 percent difference in study 1125. There was not consistently greater efficacy with one dose of tofacitinib.

The second primary endpoint in each study was the change from baseline in disability index score at month 3. This instrument assesses a patient's level of functional ability. Values range from 0 to 3, with higher values indicating a patient's increased difficulty.

The prespecified analysis was a mixed model for repeated measurement, with fixed effects of treatment, visit, treatment by visit interaction, geographic location, and baseline value. No imputation was used with this analysis, relying on

a missing-at-random assumption.

Both doses of tofacitinib in each study were associated with statistically significant improvement in physical function, indicated by a decrease in score compared to placebo.

In the comparison of the proposed dose of 5 milligrams versus placebo, there was approximately a mean difference of 0.17 in study 1091 and 0.25 in study 1125. There was not consistently greater efficacy with one dose of tofacitinib.

The ACR20 response is calculated as a greater than 20 percent improvement in tender joint count and swollen joint count in 3 of the 5 remaining core set measures. We present here the mean change from baseline in each of these ACR components with the exception of the previously presented HAQ-DI, comparing the tofacitinib 5 milligrams to placebo.

Analysis of all of the components of ACR favored tofacitinib compared to placebo, with statistically significant differences in either one

or both studies. Thus, results were generally consistent across the components.

Enthesitis and dactylitis are potential manifestations of psoriatic arthritis. To evaluate the impact of tofacitinib on these manifestations, the Leeds Enthesitis Index Score and Dactylitis Severity Score were evaluated at month 3 in patients with baseline LEI greater than zero and DSS greater than zero, respectively.

We present here the mean change from baseline in each of these scores, comparing tofacitinib 5 milligrams to placebo. In study 1125 but not study 1091, tofacitinib 5 milligrams was associated with significantly greater reductions in LEI and DSS at month 3. However, the tofacitinib 5-milligram treatment effects for change from baseline in both studies turned it in the direction of benefit.

At the time of the primary efficacy evaluations, month 3, discontinuation rates were low at less than 10 percent. To assess the impact of missing data, the applicant included several

secondary and sensitivity analyses for each endpoint. We also performed several additional analyses to fully evaluate the robustness of the results to missing data assumptions, including a tipping-point analysis for the primary endpoint.

Missing data assumptions were systematically varied until there was no longer evidence of efficacy, i.e. to identify the tipping point. The tipping-point assumptions were considered implausible, therefore indicating that the efficacy results were convincing despite the missing data.

We will now shift our attention to a discussion of the radiographic endpoint. To evaluate the effect of tofacitinib on radiographic progression of joint damage, study 1091 included the endpoint change from baseline in van der Heijde Modified Total Sharp Score, abbreviated here as mTSS.

We note that, as you heard from Pfizer, the study was not designed to evaluate radiographic progression. Furthermore, we emphasize that radiographic claims have not been required for

regulatory approval of psoriatic arthritis in the past.

However, because radiographic progression is considered an important clinical endpoint, we believe it is of interest to discuss the available evidence to support an effect of tofacitinib in inhibiting structural progression in psoriatic arthritis. We will also use this opportunity to discuss study designs and analysis approaches for assessing radiographic progression in inflammatory arthritis studies.

To begin this discussion, I remind you of the study 1091 design. You will recall that the primary endpoints were evaluated at month 3. The radiographic evaluations, however, occurred at baseline and at month 12. The endpoint was change from baseline in mTSS at month 12. Though the placebo period ended at month 3, joint damage is not expected to reverse. Therefore, any damage accrued in months 0 to month 3 while subjects were receiving placebo should have still been observable at month 12.

Thus, although the sample size was small and the placebo exposure was short, comparisons of tofacitinib against the placebo arms in this study could potentially identify a treatment effect.

In the following discussion, we will refer to the combined placebo-to-tofacitinib arm, which combines the outcomes from sequences D and E. The analysis of change from baseline in mTSS used an ANCOVA model with treatment, geographic location, and baseline value. The linear extrapolation was applied for missing data at month 12, when individuals had a baseline observation and an early termination visit.

This table shows the results from this prespecified analysis. Positive values correspond to radiographic progression, and we note that the mean changes on placebo in historical studies have often been in the neighborhood of 0.5 to 1.0.

The adjusted means observed across arms in this study are all very close to zero, indicating that very little radiographic progression was observed in this study. Each of the corresponding

confidence intervals overlap zero.

Here, we show the pairwise comparison of tofacitinib 5 milligrams to the combined placebo-to-tofacitinib arms. This comparison was not significant, and the numerical difference was close to zero. We also show the pairwise comparisons of tofacitinib 5 milligrams versus the active comparator of adalimumab. The numerical difference was also close to zero.

As I alluded to in the previous pairwise comparisons, there are two possible approaches for evaluating the evidence of effect on radiographic progression. The first approach is a superiority comparison versus the combined placebo-to-tofacitinib arm.

As discussed, there was no evidence of superiority for tofacitinib versus placebo at month 12 in study 1091, although this was not unexpected given the small sample size and the fact that patients on the placebo arm received active therapy after month 3.

The second approach is a non-inferiority

comparison to the active comparator, adalimumab, given that adalimumab has an established effect in inhibiting radiographic progression. This approach requires defining a non-inferiority margin for testing. We acknowledge that this was not the original goal of study 1091, and therefore this margin was not prespecified by the applicant.

Over the course of the next few slides, I will discuss the process of non-inferiority tests and the possible NI margin options.

In this non-inferiority test, the goal is to demonstrate that the test drug, tofacitinib, has an effect in inhibiting radiographic progression by showing that its effect is sufficiently close to the effect of the active control, adalimumab.

By demonstrating that the difference between the effect of the test drug and the effect of the active control is smaller than some pre-defined margin, the test drug is considered effective. The margin selection can be informed by data from historical placebo-controlled studies of the active control.

A non-inferiority margin should be chosen that is smaller than the effect of the active comparator versus placebo observed from historical studies. For example, one potential approach is to choose a margin based on a certain percentage of the upper bound of the 95 percent confidence interval of estimated treatment effect. This helps ensure that ruling out that margin in the NI trial establishes evidence of efficacy versus placebo.

Shown here is a hypothetical estimated treatment effect from a historical study or studies. This dashed line indicates the 95 percent confidence interval upper bound from this study. This second line indicates a possible NI margin.

The percentage of the upper bound that is chosen for this margin can vary based on clinical judgment regarding how much of the active comparator treatment effect should be retained and based on the degree of confidence in similarities between historical studies and the current non-inferiority study.

We provide here 5 different possible results

from the NI study shown as treatment effects with 95 percent confidence intervals. To achieve non-inferiority, the upper 95 percent confidence interval of the treatment effect, calculated as test minus active, must be less than the NI margin, M.

In the first scenario, the upper confidence interval bound falls below zero, demonstrating superiority of the test treatment over the active control. In the second and third scenarios, the confidence interval is below the non-inferiority margin, demonstrating non-inferiority.

In the bottom two scenarios, the upper confidence interval bounds of the treatment effect are larger than the margin. Therefore, non-inferiority cannot be concluded.

Using this approach, we considered two potential options for determining a non-inferiority margin, each with its limitations. The first option is to choose a margin informed by all historical studies evaluating effects of TNF inhibitors on radiographic progression in psoriatic

arthritis. This approach relies on the assumption that the historical estimate of effect across TNF inhibitors is a reliable estimate of the effect of adalimumab.

The second option is to choose a margin informed by only studies of the active comparator, adalimumab. There is only a single historical study evaluating the effect of adalimumab on radiographic progression in psoriatic arthritis, so this approach relies on a single study and it does not capture study-to-study variation.

In the first option, we conducted meta-analyses to obtain confidence intervals for the average estimated treatment effect of TNF inhibitors. In these historical studies, the placebo arm ended at month 6 with subjects on this arm crossing over to the active experimental treatment arm. Therefore, we base the NI margin considerations on the meta-analysis of month 6 mean change from baseline in these studies.

Given that radiographic damage is expected to progress over time in the absence of effective

treatment, estimated treatment effects at month 6 are likely conservative estimates of effects at month 12, the time point of radiographic assessment in study 1091.

For this meta-analysis, we relied on published estimates, standard deviations, and sample sizes from 4 TNF inhibitors previously studied for effect on radiographic progression, adalimumab, etanercept, infliximab and golimumab. The mean change from baseline in mTSS in each of these studies was positive on the placebo arm, indicating progression of joint damage, and was close to zero on the experimental treatment arm, consistent with a lack of progression.

Using the fixed effects or random effects meta-analyses of these historical studies, the treatment effect estimate is approximately minus 0.7 with an upper 95 percent confidence interval bound of approximately minus 0.5.

As stated, non-inferiority margins can be chosen based on some percentage of a conservative estimate of the effect of the active control. For

example using 25 to 75 percent of the upper confidence interval bound from the meta-analysis of TNF inhibitor studies leads to non-inferiority margins in the range of approximately 0.125 to 0.375.

This range of possible margins is shown by the blue dashed lines. The observed 95 percent confidence interval from the tofacitinib 5 milligrams versus adalimumab comparison in study 1091 was minus 0.08 to 0.25. Therefore, the upper confidence interval bound of 0.25 for the tofacitinib 5-milligram dose, shown in red, rules out only those potential margins with minimal conservatism built in.

Alternatively, the NI margin can be informed by the adalimumab study alone. In this study, as reported in the Humira label, the estimated treatment difference in change from baseline in mTSS of adalimumab versus placebo was minus 1.0 with a 95 percent confidence interval of minus 1.60 to minus 0.40.

Using 25 to 75 percent of the upper

confidence interval bound from the adalimumab study alone leads to NI margins in the range of 0.1 to 0.3. This range of possible margins is shown by the orange dashed lines. The observed 95 percent confidence interval from the tofacitinib 5 milligrams versus adalimumab comparison in study 1091 was minus 0.08 to 0.25. Therefore, again, the upper confidence interval bound of 0.25 for the tofacitinib 5-milligram dose, shown in red, rules out only those potential margins with minimal conservatism built in.

Using either option for defining a non-inferiority margin, the comparison between tofacitinib and adalimumab with respect to radiographic progression rules out only those potential NI margins with minimal conservatism. This is problematic because there are several additional considerations which support the use of a more conservative margin.

First, we note that there is only a single study evaluating the effect of tofacitinib on radiographic progression. Furthermore, we consider

the current study's similarity to historical studies and its sensitivity to identifying the true differences between tofacitinib and adalimumab.

The concern is that if the adalimumab-controlled study was conducted in a setting in which minimal progression was expected on any treatment arm, a lack of differences between arms might reasonably be expected even if tofacitinib were truly inferior to adalimumab and ineffective in inhibiting radiographic progression.

To address these concerns, we compared the amount of placebo progression and the values of prognostic baseline patient characteristics of study 1091 to historical studies of radiographic progression.

We compared the current study with seven studies of bDMARDs in psoriatic arthritis with month 6 radiographs. The placebo mean changes at month 6 ranged from 0.2 to 1.0 with the mean progression greater than 0.5 in 5 of the 7 studies.

Patients in study 1091 received placebo for only 3 months rather than the 6-month or 1-year

periods in these historical studies. However, the results indicate the mean levels of progression observed in study 1091 across the treatment arms were much lower than those in previous studies.

Furthermore, the current study population differed in its baseline characteristics relative to populations of previous studies. In particular, the mean baseline CRP values and mean baseline modified total Sharp scores were lower than most of the previous studies.

These baseline characteristics have been previously identified as prognostic factors for progression, indicating this study may not have been adequately designed to observe progression on any arm, and therefore may not have had sufficient sensitivity to detect true differences between products.

It is particularly notable that the historical study of adalimumab had both considerably greater mean progression on placebo and higher mean values of baseline CRP and modified total Sharp score than study 1091.

The lack of progression observed on tofacitinib in study 1091 is consistent with the potential effect on radiographic damage. However, our evaluation of the design and results of the study indicated there is insufficient evidence to support a claim for inhibition of radiographic progression.

First, the superiority comparison of tofacitinib to placebo did not show evidence of a treatment effect. Second, the NI comparison of tofacitinib against the active comparator, adalimumab, in a single study does not persuasively rule out an appropriate non-inferiority margin. Reliance on a single non-inferiority study to support a claim would require convincing statistical evidence and robust conclusions.

Finally, the lack of progression observed on the placebo arm and the patient and design characteristics of study 1091 versus those aspects of historical studies lead to questions about the sensitivity of the study to detect true differences.

We do note, however, that larger active controlled studies in populations enriched for progression and with additional rigorous discussion about appropriate NI margins may provide more persuasive evidence of drug effects on radiographic progression in psoriatic arthritis.

To conclude, we find that the symptoms and physical function results described here are highly supportive of the effectiveness of tofacitinib for treatment of psoriatic arthritis. While the totality of the radiographic analyses and evaluation does not provide substantial evidence that tofacitinib doses have an effect in the inhibition of radiographic progression, we again note that evidence of such an effect has typically not been considered necessary for approval for drugs to treat psoriatic arthritis.

In study 1091 and study 1125, treatment with tofacitinib 5 milligrams provided statistically significant absolute differences over placebo for the first primary endpoint, ACR20 response probability at month 3 and the second primary

endpoint of mean change from baseline and HAQ-DI. Our supportive and secondary analyses as well as those performed by the applicant generally supported a benefit.

I will now turn over to Dr. Nair for the summary of safety and risk-benefit considerations.

FDA Presentation - Raj Nair

DR. NAIR: Tofacitinib has been approved for use in rheumatoid arthritis and carries boxed warnings as well as several warnings and precautions. Among these risks are infections, malignancies, and lab abnormalities. In the psoriatic arthritis program, the adverse events seen were consistent with the findings in the prescribing information, shown here.

At the time that tofacitinib was approved for use in rheumatoid arthritis, the FDA asked for a long-term safety trial to evaluate for safety events of interest as part of a postmarketing requirement. Adverse events of special interest included cardiovascular events, opportunistic infections, and malignancy.

The estimated primary completion date for the trial is August 2019. The trial is ongoing with an estimated enrollment of over 4,000 patients.

In the psoriatic arthritis program, there were approximately 800 psoriatic arthritis patients exposed to at least one dose of tofacitinib. While we are focusing on the safety of tofacitinib in psoriatic arthritis, it is important to note that the safety is informed by additional information from other indications, including rheumatoid arthritis and psoriasis. The exposure in the rheumatoid arthritis and psoriasis programs was much higher than in the psoriatic arthritis program.

In general, the adverse events seen in the psoriatic arthritis program were consistent with what has been seen in the prescribing information for tofacitinib.

We will focus on the following adverse events of special interest: deaths, serious adverse events, malignancies, serious infections, herpes

zoster, opportunistic infections, and major adverse cardiovascular events.

The study cohorts provided in the psoriatic arthritis supplemental application are shown here. Cohort 1 was a placebo-controlled period for 3 months. The comparisons were with tofacitinib, 5 milligrams twice a day, tofacitinib, 10 milligrams twice a day, and placebo.

Cohort 2A provides comparisons of the two doses of tofacitinib with data collected up to 12 months in studies 1125 and 1091. I will be presenting safety from events that were collected on patients who were randomized to a dose of tofacitinib as well as patients who were initially randomized to placebo, but later exposed to tofacitinib at 3 months, after the placebo-controlled portion of the study was completed. These group of patients will be labeled as all tofa 5 and all tofa 10.

Cohort 3 pools data from patients who were exposed to tofacitinib at any dose from studies 1125, 1091, and 1092. This group will be referred

to as all tofa all doses in the upcoming slides.

There were no deaths reported in the 3-month placebo-controlled period, and there was one death in the first 12 months reported. A total of 4 deaths were noted in the all tofa all dose group.

The causes of death are shown in this table. The cumulative days on tofacitinib are shown in the column furthest to the right. The causes of death were sudden cardiac death, pancreatic cancer, hypertensive heart disease, and large bilateral pulmonary embolism. All patients who died were exposed to tofacitinib at some point during the trial period.

SAEs during the placebo-controlled period of the pooled psoriatic arthritis studies are shown here. The incidence rate of patients with an SAE was similar in each tofacitinib arm and in the placebo group. The incidence rates stayed stable through the 12-month period and beyond.

Overall, in the psoriatic arthritis program, the incidence rate for serious adverse events was 8.5 events per 100 patient-years.

For malignancy, there were 2 malignancies in the placebo-controlled period. At 12 months, there was one additional malignancy. In total, there were 5 malignancies and all occurred in patients who were on 5 milligrams of tofacitinib. The incidence rate for malignancies in the all tofacitinib all doses group was 0.6 events per 100 patient-years.

The malignancies that occurred during the all tofa all doses time period are shown here. The malignancies that occurred were transitional cell carcinoma of the bladder, renal cell carcinoma, metastatic pancreatic carcinoma, squamous cell carcinoma of the vulva, and invasive ductal breast carcinoma.

The cumulative days on tofacitinib are shown in the column on the far right along with previous adalimumab usage if applicable.

Serious infections are presented here. Two serious infections occurred in the placebo-controlled period, both in the 10-milligram dose group. At 12 months, the rate of serious

infections was similar in both dose groups. In total, there were 11 patients with serious infections in the psoriatic arthritis program with an incidence rate of 1.4 per 100 patient-years.

Two events of herpes zoster were noted in the 5-milligram twice-a-day tofacitinib group, and one event was noted in the 10-milligram twice-a-day group during the placebo-controlled portion of the psoriatic arthritis studies. No events were noted in the placebo group. In the 12-month period, additional events of herpes zoster were seen within the tofacitinib groups.

In all, 16 patients had events of herpes zoster in the tofacitinib groups with an overall incidence rate of 2.1 per 100 patient-years.

In the 3-month placebo-controlled period, there was one opportunistic infection for a patient taking 5 milligrams twice a day tofacitinib. In the all tofa all doses cohort, 3 patients on tofacitinib were classified as having an opportunistic infection. All of the opportunistic infection cases were multidermatomal zoster. No

cases of tuberculosis were seen in the psoriatic arthritis program.

Major adverse cardiovascular events were not seen in the 3-month placebo-controlled portion of the pooled studies. During the 12-month period, there was one event in the 5-milligram twice-a-day group and one event in the 10-milligram twice-a-day group. A total of 3 major adverse cardiac events were reported in the whole psoriatic arthritis program.

Study 1091 had an adalimumab comparison arm. Comparisons are shown at 12 months for the doses of tofacitinib and adalimumab for selected adverse events of special interest. The number of events were small. In general, there appeared to be a slight numerical increase in adverse events of special interest when taking tofacitinib compared to adalimumab.

While a few adverse events were presented in the safety presentation, the other known warnings and precautions labeled in the tofacitinib prescribing information were seen in the psoriatic

arthritis program.

In general, adverse events seen in the psoriatic arthritis program were similar to the known safety profile for tofacitinib. Adverse events related to immunosuppression such as serious infections and herpes zoster were seen.

Malignancies, major adverse cardiovascular events, gastrointestinal perforation, and laboratory abnormalities were also seen in the psoriatic arthritis development program.

I will end with a slide on overall risk and benefit considerations, which may be helpful to the committee's discussion for the overall efficacy and safety of tofacitinib in psoriatic arthritis.

Benefits of tofacitinib for psoriatic arthritis included superiority to placebo for physical function and signs and symptoms. Based on the radiographic data provided, there is not substantial evidence that tofacitinib has an effect on radiographic progression.

The risks are similar to the known safety profile of tofacitinib and include serious

infections, herpes zoster, opportunistic infections, malignancies, GI perforations, and various lab abnormalities. This concludes my presentation. Thank you.

Clarifying Questions

DR. SOLOMON: Thanks very much.

We now have some time for clarifying questions, so please remember to state your name when you're speaking. Erica Brittain and then Michael Weisman.

DR. BRITTAIN: Erica Brittain. I have a question about Dr. Rothwell's presentation. First of all, I just want to make a comment. I guess it's obvious that your conclusions about the non-inferiority are not a knock on the current study because it wasn't powered to detect it.

You focused on a number of reasons why non-inferiority is really a challenge for statisticians to design. I have a couple questions. First, on slide 33, I'm not quite sure I was following this. I mean, I understand the importance of being able to -- you have to know that a study can detect

differences, and that's an important principle, underpinning a non-inferiority design.

But I wasn't quite sure I understood the point you were making here. I mean, obviously the fact that these baseline variables are so different from these historical data -- that is important in itself, but I wasn't quite sure I was understanding the point you were making here. And I have one follow-up question after that.

DR. ROTHWELL: Sure. So I think there are two points that we are covering here. One is if we would see progression in this group of patients, so is this study designed to see any difference in progression. And then second, is this constancy assumption; when we're looking across for non-inferiority studies, looking at comparing to the adalimumab placebo-controlled study, if there are enough similarities there to maintain that constancy assumption.

DR. BRITTAIN: The treatment effect is constant. Is that what you mean by the constancy assumption, that the treatment effect is constant

across studies?

DR. LEVIN: That the estimate of the effect of adalimumab from the historical studies would be a reliable estimate of the effect of adalimumab in this study if there were a placebo arm.

DR. BRITTAIN: Okay. Yes, right.

DR. LEVIN: So the fact that there were lesser average values of baseline characteristics that are known prognostic factors for radiographic progression makes us question that a little bit.

Then also the fact that you observed very minimal progression on the placebo arm at month 3 with the caveat that the historical studies looked at placebo at month 6, the .04 is still much, much, much smaller than what was observed at month 6 on placebo as an average amount of progression with all the limitations of cross-study comparisons, but this is the data that we have to work with.

DR. BRITTAIN: Of course, if you were designing a study ahead of time for a non-inferiority endpoint, you wouldn't know this. Right? I mean, you could only sort of do this

after the fact, correct? Because this is for the current study.

DR. ROTHWELL: This is for the current study. If you were designing ahead of time, though, you could look for these prognostic factors.

DR. LEVIN: You could enrich your study for progression by, for example, having inclusion criteria that tries to -- and you'd be okay doing that in a setting where you don't have a placebo arm, for example.

I think there was rightfully reservations about doing that with a placebo arm in the study and also based on feedback from FDA during the development about doing that. But in an active control study where you don't have a placebo arm, you could try to design your study in a setting where you expect progression in the absence of an effective therapy.

DR. BRITTAIN: Finally, I guess I was a little confused about what would be the role of this? Is it for sort of a special additional claim

or would it be potentially a primary endpoint? I wasn't quite sure what the whole role of these analyses would be.

DR. MAYNARD: So generally, the program for psoriatic arthritis, as was mentioned by Pfizer, have focused on signs and symptoms and physical function as the primary basis to support approval. But also frequently, sponsors will look at radiographic endpoints, and if there is convincing evidence of efficacy, that could potentially be included in the labeling as a separate claim. But it is not necessary to support approval for psoriatic arthritis, which is primarily based on the evidence of effect on signs and symptoms.

DR. SOLOMON: Michael, and then we'll move on.

DR. WEISMAN: I had a similar question to ask the FDA about the non-inferiority issue. And I can't talk statistics. I'm just a poor country doctor from Beverly Hills.

(Laughter.)

DR. WEISMAN: It looked to me like when you

looked at the adalimumab data, those patients in the historical controls were sicker and more likely to progress, and patients in this study were less sick, less likely to progress. So it's not possible to really understand radiographic progression in this population easily.

Did I get that right?

(Dr. Rothwell nods yes.)

DR. WEISMAN: So what implication does that have on an analysis of the rest of the study, that the adalimumab group was a little less sick? When you look at the overall comparison for safety and efficacy clinically, what's your impression of that, and does that impact in any way your interpretation of the efficacy and safety of this population that was studied?

DR. LEVIN: So you're talking about the rest of the comparison against adalimumab, not against placebo from the rest of the studies?

DR. WEISMAN: Right.

DR. CHOWDHURY: I'm Dr. Chowdhury here, just to take your question, and then Janet or somebody

else can add on to it. I think there are two points here that we're trying to separate out, the primary basis of approval generally could be on signs and symptoms and physical function, and we have that. The other piece is radiographic progression, which is a different, as was mentioned, claim, which is an important claim.

As far as the comparative assessment for overall safety goes, we have a reasonable placebo treatment arm for reasonable duration based on which one can make a conclusion. So that piece is there.

As far as radiographic progression, which we heard earlier is what we're trying to bring up, is a non-inferiority trial is essentially trying to replicate what was done historically before in a similar patient, a similar design as much as practical so that you can assume what the placebo effect would be with the placebo not being there.

In this study, what we have, for good reasons, is that the patient population enrolled with lesser CRP numbers, lesser baseline erosions,

and other factors that can predict extra progression, in this current study, those patients were not there.

So therefore, you would not generally expect, even if there was a placebo, to progress much. But we don't have a placebo here, so you are making an assumption.

So that's the problem that we have is you really cannot necessarily use the study to link the previous study to conclude both the drugs do not have progression. What you see here, both the drugs did not have progression, is not to say that progression could not have happened.

It's a good thing that we saw -- that if we had seen the progression in the tofacitinib, for example, in the study, we'd be a bit more cautious. We didn't see it, which is pretty good. The point we're trying to raise is it is not designed, fully understood, with a non-inferiority design in consideration. But if we apply the standards, this one doesn't seem to make it.

Janet?

DR. MAYNARD: Just to add that these patients did have active psoriatic arthritis, so we thought it was a reasonable patient population within which to evaluate the efficacy and safety of tofacitinib for active psoriatic arthritis. And as was mentioned, the point of these analyses was more to think about it in the context of the understanding of the radiographic progression in the study and not to criticize that the study population was in some way unable to assess the efficacy and safety of tofacitinib.

DR. SOLOMON: Just before we go on, just to be clear, there is no claim from the sponsor on radiographic.

DR. CHOWDHURY: Yes. I think the claim is a tricky question because what we consider anything in the product label anywhere could be a claim, including describing a study with a finding in section 14, which is the clinical trials section. So that is the way we look at a claim.

So the question that we're discussing here, and we would like your opinion certainly on is, is

the study one can rely on to conclude that tofacitinib has no effect or has an effect on radiographic progression? So there is potentially a claim depending on how we look at the study.

DR. SOLOMON: But what I heard from the sponsor was that they had no hypothesis.

DR. CHOWDHURY: That is correct, and that is the reason for bringing it up. If there's no hypothesis, no formal testing, but you find the results, does it give you enough confidence to conclude that tofacitinib has a beneficial effect on the natural radiographic progression. So that's the question that we're raising here.

DR. SOLOMON: Maria?

DR. SUAREZ-ALMAZOR: Yes. I had a couple of questions related to that as well. I mean, for other approvals before and for other drugs, this has not been required, this non-inferiority margin and so forth. So I'm not really sure why now, after the fact, if it was not required a priori we are making such a big deal of this.

I think there has been in other labels

before some statements about radiologic progression for other diseases, rheumatoid arthritis or whatnot, or other agents, and those were allowed to be carried forward without any other requirements related to non-inferiority. So that's my first question.

The second one relates to the clinical significance of all of this. And I had to go back to the van der Heijde Sharp score to make sure that I presented my question in the right way.

If I understand correctly, the way this is scored, you have 16 joints per hand for erosion and 15 areas for joint narrowing. For the erosion, it's 1 to 5, and for the narrowing, it's 1 to 4. So 16 per hand plus 15, so that takes us into almost 100 areas that are scored and 0 to 5 or 0 to 4.

We are talking about a margin of 1, so in the context of what this is, we are talking 32 joints for erosions, and it would be one joint going from 1 to 2. So what's the clinical significance of that?

So I think we are putting requirements that we don't even know if they have any significance in the big picture, a change in a score of 0 to 5 in one joint when we are measuring 32 joints. I mean, what's the clinical significance of that? Should we really be looking at that when we don't have a good clinical correlate?

DR. MAYNARD: So in terms of your first question regarding if we're saying that non-inferiority comparisons are required, we're not intending to say that these are required. We really just looked at the data that was available to us and tried to see whether we could see persuasive evidence of efficacy either on superiority or non-inferiority.

But our intention is not to say that this is required for approval because, as you mentioned, for other approvals, for the inflammatory arthritides, that has been based on signs and symptoms, and some sponsors have chosen to also evaluate radiographic progression. But that's really a choice that sponsors can make and that we

have not historically required. So I think we're in agreement with your point.

In terms of the second point about what's the clinical significance about this, I think we would welcome committee input on that subject. It seems that, previously, there has been interest in evaluating the effect on radiographic progression, but if the committee feels that that is not necessarily important information, we welcome feedback about that.

DR. SUAREZ-ALMAZOR: I'm not saying that it's not important information. I'm saying that, when you get into a margin and you're going to such a small value, I don't know that it has clinical relevance. Again, I don't know if in the description of the study in the label, one can say -- and that goes more to my first point -- were no significant differences between adalimumab and tofacitinib if now you are requiring to say this, we want a non-inferiority trial, which was not required in the past.

So now you may require that, but that would

increase the number of patients for a study tremendously, and I don't know that to find a difference of a score of 1 it would be worth it because we don't know that that's clinically relevant with respect to prognosis or differences later on. It's important to learn from a structural perspective, but I don't know that it's clinically relevant.

DR. MAYNARD: Just to clarify, we are not saying that this is required, just to clarify that point, just that we evaluated the evidence of efficacy based on non-inferiority, given the fact that this was an active comparator study, but it's not required.

DR. SOLOMON: James, Diane, and Erica. No Erica. James and Diane.

DR. CHUNG: I think we recognize that this actually is quite important for both the physicians and the patients to be able to confidently demonstrate it and importantly also to communicate it to both of those audiences.

I think we also recognize some minority

patients who have the progression, so although I think in the aggregate, the impact may be small for certain patients, as Dr. Mease has shown, the impact can be pretty significant on an individual basis. So I think all of these are important.

If we can go back to slide 33 that we started with, I think one of the ways in which it could show a difference is to look at the historical control. I think what's striking about this particular table is, yes, the CRP and the mean Sharp scores are lower than the adalimumab study for the 1091, but such a much lower placebo progression there, as you noted, is because of some of the limitations of the trial design.

But although the numbers are lower, I think the majority of the patients in this trial actually had elevated CRP and pre-existing erosions, which is an enrichment of patients who will progress. So I do wonder what the true effect is, and if I had to guess, I would think it would be closer to 0.9 than what we see there on the table.

I wondered whether the FDA had looked at, or

considered looking at, historical cohorts, matching the patients, to the best of your ability, for the CRP Sharp score and perhaps other baseline characteristics.

DR. LEVIN: We have not looked at that.

DR. CHUNG: But thinking about sort of future and other agents that may also come in for this, would there be value or how would you look at developing a robust data set that we could draw on for progression, natural progression of these placebo subsets that are perhaps matched for these important baseline characteristics?

DR. LEVIN: So it's a good question. I think we also want feedback from the committee on this kind of an approach, for example if Pfizer was to do another study to evaluate the effect of tofacitinib on radiographic progression.

But I think, as Dr. Rothwell mentioned, doing it in a setting where you expect progression, where you're enriching it for progression, I think gives you a little bit more confidence that the study might be sensitive to identifying differences

between products if those differences exist.

DR. SOLOMON: Diane Aronson?

MS. ARONSON: From a patient perspective, anytime I visited rheumatologists, the number one thing they always say is you have to do something to prevent structural damage. So from a patient perspective, this becomes really important as an individual patient evaluates options.

I also appreciated Dr. Chung's comment about minority changes in joint damage. This study of over 300 patients had 3 African-Americans in it. And I understand the challenges with clinical trials, but I also think about that in relationship to a broader community that may be potentially using this.

DR. SOLOMON: I think we have had a lot of good discussion and clarifying questions. We'll have more time for discussion later on. So we're going to move to a break for 15 minutes, so we'll come back at five minutes until 11:00 and continue.

(Whereupon, at 10:41 a.m., a recess was taken.)

Open Public Hearing

DR. SOLOMON: While people are taking their seats, we're going to move towards the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency of the open public hearing session of the advisory committee meeting, 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 today's 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 chairperson, 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 morning, nice to see everyone again. My name is Stephen Marmaras. I'm the director of state and national advocacy for the Global Healthy Living Foundation. Thank you for a really informative discussion again thus far. I just wanted to mention that I have no disclosures to make regarding my travel here today.

On behalf of the Global Healthy Living Foundation, I want to thank this committee for allowing me to speak. 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.

GHFL represents more than 100,000 chronically ill patients and their caregivers across the country. Many of these individuals are part of our online arthritis community, CreakyJoints and have psoriatic arthritis or other related autoimmune diseases, and have had their

lives changed by biologics.

Our patient community knows we speak on their behalf to the FDA, and they don't hesitate to tell us what they think we ought to say. GHLF believes that patients should be valued as citizen experts on the drugs they take. We seek to amplify their voice, and that's what I'll try to do today, by relaying their commitment to learning and engaging with larger audiences like this one.

Our patient community over and over again tells us about the debilitating nature of their disease and their fear of losing physical independence. They look to medical treatments not only to remedy their pain, but to greatly improve their quality of life.

Yesterday, I relayed to FDA the concerns of Judy in Sandusky, Ohio, Lisa in Lake Stevens, Washington, and Rick in Indianapolis, Indiana. These people have tried many biologics. While these medications can have a dramatic positive impact on people's well-being, a biologic's effectiveness varies from individual to individual.

Some work for only a short period of time and some have caused intolerable side effects.

We have found that the majority of patients in our community try 4 or 5 biologics before achieving stability. We support the speedy approval of safe and effective tools, as there is a great need for additional medical options for patients unable to find a suitable treatment.

We believe tofacitinib positively impacts many issues that our patient community cares about. They are as follows.

Number 1, new method of action for psoriatic arthritis. Rheumatologists, dermatologists, 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 therapy that works for them as an individual is not an easy one. There is a lot of trial and error involved, and patience and persistence are key.

We know that, when you transition patients with autoimmune diseases between therapies, there's

a likelihood of different responses, so patients are excited about potentially having the first JAK inhibitor available to address psoriatic arthritis. Patients are hopeful that tofacitinib will offer another safe and effective option as a resource for their physician to consider.

The second is, route of administration we believe will promote compliance. People living with autoimmune diseases tell us that medication taken orally are preferable for several reasons. Among them are needle phobia, convenience and mobility challenges associated with not having to travel, to arrange transportation to an infusion center or doctor's office to receive assistance in using self-injector devices, and not needing to worry about special storage and handling instructions.

We know that psoriatic arthritis patients in our community are generally 10 years younger than the average RA patient, and with that comes a stronger preference and value on being able to maintain active and independent lifestyles.

Without the constraints of cold-chain requirements, travel is easier, and compliance we believe is more likely.

Lastly, encouraging clinical trial details. Our members with psoriatic arthritis overwhelmingly prioritize joint pain and stiffness as the most bothersome symptoms they experience. The symptoms associated with the skin are incredibly difficult to live with as well and pose their own challenges to individuals' personal and professional lives, but those in our community particularly emphasize their joint degradation.

They are fearful because the skin can heal, but joint damage is irreversible. With that in mind, we were encouraged to read that tofacitinib has particularly notable efficacy in treating the joint symptoms of the disease in clinical trials. Patients value therapies that work quickly. We were encouraged to learn that the primary endpoint was an aggressive 3 months for this drug.

Lastly, we discussed the younger demographic living with this disease, but there is also a fair

percentage of our community that are elderly and living with psoriatic arthritis. For these individuals that we represent, we believe the drug's shorter half-life can be beneficial to them, as they are more likely to need to cycle off therapy quickly to prepare for surgeries or battle infections.

Once again, we want to relay that we always put our faith and trust in the experts at FDA to keep our patient community 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 addition as a new mechanism of action to treat the disease and its likelihood to promote therapeutic compliance.

We thank the FDA for emphasizing the value of the patient perspective through public meetings like this one. Thank you for your time and attention and allowing me to speak.

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.

DR. HOWARD: My name is Richard Howard. I'm the associate executive director of the Spondylitis Association of America.

Good morning. I'm grateful for the opportunity to speak today. Thank you. The Spondylitis Association of America, we encourage you to approve additional medications that are safe and effective for treating psoriatic arthritis.

The Spondylitis Association of America is the only nonprofit patient advocacy organization in the United States which dedicates its resources to advancing spondylitis arthritis research and providing educational programs and support services that enrich the lives of those living with ankylosing spondylitis and related diseases such as psoriatic arthritis.

For over 30 years, the SAA has been at the forefront of major advancements in research, education, and advocacy for AS related diseases. As a premiere and trusted resource of spondylitis, SAA is the first place patients, families, and

friends turn to for accurate and up-to-date information.

This hearing is particularly important to the Spondylitis Association of America and the 2.7 million Americans living with actual spondylitis arthritis that the SAA serves due to the unmet needs of the current array of indicated medications.

Twenty-eight percent of the 600,000 Americans with psoriatic arthritis will develop psoriatic spondylitis that affects the spinal column from the neck to the lower back, and when untreated can lead to permanent damage to the joints. As in ankylosing spondylitis, inflammation of the spine can lead to complete fusion and affect only certain areas such as lower back and neck, and we don't fully understand which one of us will progress.

Treatments have advanced in the past 20 years, but we're not there yet. We need to continue to have options and access to save and effective medications. In my role at SAA and as a

leader of the local education support group in Los Angeles, I speak with people whose needs are not met with the current few mechanisms.

I wanted to introduce Kelly, who is on her way here, who was originally diagnosed with psoriatic arthritis in her senior year of high school, and has been living with it for nearly 11 years.

"For me, the disease causes acute pain in my hips as a preteen. A misdiagnosis led to hip surgery at 21. The chest, shoulder, and spine pain would wake me up at 4:00 a.m., and by the time I was diagnosed at 28, I had permanent damage to my SI joints and was told that hip replacements were a certainty. I have ulcerative colitis and uveitis, and additional permanent damage in my cervical spine."

Our work at the SAA will not be finished until everyone with spondylitis arthritis are able to live life to the fullest, often with the assistance of medications, and until we find a cure and a way to prevent the next generation from

getting this ancient disease.

Thank you for consideration to continue to improve safe and effective medications that give treatment options to patients as they come through the pipeline. Thanks again.

DR. SOLOMON: Thank you. Will speaker number 3 step up to the podium. Speaker number 3 is not here.

So the open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand.

Before we get to that, we would like to give Pfizer a minute to clarify a point on the radiographic data.

DR. MAYNE: Thank you, Mr. Chairman. James Mayne, Pfizer. I just wanted to make three quick points that may assist in your consideration of the discussion regarding the progression data.

The first point is that our existing product label includes a structural benefit progression

evidence section based on data obtained from rheumatoid arthritis patients.

The second point is that, as noted earlier, we conducted the study and included a progression endpoint, not as a hypothesis-testing exercise, but rather to provide confirmatory and reassuring evidence that patients are not progressing while on treatment.

We believe that the study accomplished that objective, and based on that, we also believe that that information is useful to prescribing physicians, and therefore have proposed in our proposed label language that information be included. I hope that's helpful.

DR. SOLOMON: Thank you.

I'm going to have Dr. Maynard now provide us with a charge to the committee.

Charge to the Committee - Janet Maynard

DR. MAYNARD: As we prepare for the committee discussion and voting today, I wanted to provide a brief reminder of the issues, the regulatory framework for FDA's standards for

approval and non-approval of a marketing application, and the questions to be discussed and voted upon.

As mentioned earlier, the submitted data provide evidence of tofacitinib's efficacy for signs and symptoms and physical function in psoriatic arthritis. However, the totality of the data does not provide substantial evidence that tofacitinib has an effect on radiographic progression.

It is important to note that evidence of radiographic benefit has not been considered necessary for approval for drugs that treat psoriatic arthritis.

In general, the safety profile of tofacitinib in psoriatic arthritis appears consistent with the known safety profile of tofacitinib in rheumatoid arthritis. Tofacitinib was associated with adverse events related to immunosuppression such as serious infections and herpes zoster. In the psoriatic arthritis clinical program, there were also malignancies, major

adverse cardiovascular events, GI perforation, and laboratory abnormalities.

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 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 the three scenarios which could underlie a 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 the results show 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.

Question number 1 is a discussion question. Discuss the efficacy of the proposed dose of tofacitinib for adult patients with active psoriatic arthritis. In your discussion, comment on the following, first, the overall efficacy of tofacitinib with respect to signs and symptoms and physical function for adult patients with psoriatic arthritis; next, the evaluation of the effect of tofacitinib on radiographic progression in psoriatic arthritis.

Question number 2 is also a discussion question. Discuss the safety of tofacitinib for the treatment of adult patients with active psoriatic arthritis.

Question number 3 is a voting question. For

this question, you will vote on whether, overall, the data provide substantial evidence of the efficacy of tofacitinib for the treatment of adult patients with active psoriatic arthritis. If not, what further data should be obtained?

Question number 4 is a voting question related to safety. Specifically, the question is, is the safety profile of tofacitinib adequate to support approval of tofacitinib for the treatment of adult patients with active psoriatic arthritis? If not, what further data should be obtained?

Finally, question number 5 is a voting question related to approval. The specific question is, do you recommend approval of the proposed dose of tofacitinib for the treatment of adult patients with active psoriatic arthritis? Since this is a risk-benefit question, you may wish to consider your previous voting for the efficacy, question number 3, as well as the safety, question number 4, to be consistent. In other words, to vote yes to this question, you probably should have voted yes to questions number 3 and 4.

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

Questions to the Committee and Discussion

DR. SOLOMON: Great. Thank you, Janet.

So let's bring up the first discussion question. I just want to remind folks that we'll be talking about efficacy. The radiographic progression information, which has consumed a fair amount of our conversation, is not required for approval of a drug for this indication, but it's clearly something that the sponsor is interested in as part of the claim. So it's worthwhile discussing the item, but it's not really required for approving the drug for psoriatic arthritis, just so we're clear.

So we'll discuss efficacy, and then safety, and then we'll be voting on those afterwards. Anyone want to start on A, the overall efficacy of tofacitinib with respect to signs and symptoms and physical function for adult patients with psoriatic arthritis? Michael?

DR. WEISMAN: It appears that the sponsor

has met this claim with sufficient data in my opinion.

DR. SOLOMON: Any thoughts on that issue? So the primary endpoints were the ACR20 and the HAQ-DI. There were other endpoints measured, pretty consistent across endpoints, so we don't have to belabor it.

(Laughter.)

DR. SOLOMON: We can talk. I have lots of thoughts.

DR. MEISEL: Steve Meisel. I think the data are obvious.

DR. SOLOMON: You think the --

DR. MEISEL: The data are obvious.

DR. SOLOMON: Okay. That's good.

(Laughter.)

DR. SOLOMON: Should we discuss that?

(Laughter.)

DR. SOLOMON: I think the secondary endpoints, the PRO data, are interesting. It's interesting to see the PASI in the setting of psoriatic arthritis application. Even though we're

focused on the arthritis aspect of it, the PASI data are also interesting to look at. I don't know if there's any discussion, however. That's okay.

I'm sure we'll have some discussion on point B, the evaluation of the effect of tofacitinib on radiographic progression in psoriatic arthritis; again, remembering that this is not required for the approval, but it's something that may be in the claim. I think the agency would like our thoughts on this issue.

Erica, and Michael, and Jennifer?

DR. BRITTAIN: I agree with the FDA's analysis that the lack of clear-cut evidence that we can glean from historical data to support a non-inferiority conclusion, it's a conservative approach, but I think rightly so.

I was feeling that way even before I recognized that the population was less sick and that that raises a very important concern about the applicability of the margins that you were first talking about.

I just wanted to make -- again, I think I

said this earlier. It's not a knock on the results of this study because it wasn't powered for this design.

Just in terms of a few comments about potentially using this in the future, which I think is what you want us to talk about, as an overall comment, it's good not for the primary endpoint, because non-inferiority is always hard, and it seems particularly hard here.

For the non-inferiority paradigm to work, a new study has to mimic all the study features of the historic data, and I don't know how possible or plausible that is in this setting. Especially here, when you saw that that placebo progression was so much less -- I don't know if in future studies you would presumably have a placebo phase so you could do a short-term placebo evaluation, say, at 3 months.

In a sense, if that would be the design, you would have that opportunity to look at that progression, and perhaps that would allow you to adjust your margin. It's not the way things are

usually done, but it may be something to consider and even to look at the effect -- in the study, you would be able to look at the active control versus placebo at that early time point and a study drug versus placebo.

Perhaps that could be used. Again, it's not what we would normally do in non-inferiority, but it might be something to consider.

DR. SOLOMON: Before we go on, I just wanted Erica to clarify one issue. You said it would be difficult to use the historical controls because it would be hard to select the same or similar patient population. Can you just be more explicit about that?

DR. BRITTAIN: You mean in talking about future studies and how to design it?

DR. SOLOMON: Yes

DR. BRITTAIN: Again, the non-inferiority paradigm uses historical data to estimate a very conservative estimate of how much an active control is better than placebo, and you have to then make the assumption that in your new study, it would

have the same effect; the active control would beat placebo by the same amount if placebo were in there. So studies would have to be designed the same way. They'd have to have the same background therapy, which I don't know would be the case.

DR. SOLOMON: Yes. So I think the change in background therapy perhaps is the key issue to think about.

DR. BRITTAIN: Yes.

DR. SOLOMON: But in the past, placebo might have been true placebo, and now it's placebo on top of some potentially active therapies, so there's changing paradigms of treatment.

DR. BRITTAIN: That's why I thought perhaps that short-term placebo progression could help calibrate things, but I don't know.

DR. CHOWDHURY: Can I comment, please? I think it is an important discussion for us to hear, and the point of the discussion that is going in that direction is very good for us to hear.

I just wanted to get a better understanding from the committee, why the background therapy

would be different now compared to 4 or 5 years ago, because all of these trials allowed background conventional DMARDs.

The point for the non-inferiority is really to have patients reasonably similar to what has been historically. And the two points that come up in a lot of these studies is the CRP and the background on enrollment, radiographic findings at that point, primarily erosion.

So do you think as a committee that has changed, that you would not find patients who have high CRPs or who have erosions? Are we there yet? I think it's a very subjective point, but it's worth thinking about it because industry and others may like to go in this direction, and what is the committee's thought on this? Thank you.

DR. SOLOMON: Does anyone want to -- Maria, do you want to?

DR. SUAREZ-ALMAZOR: Yes. I had a comment again on the non-inferiority. Again, I don't know what the wording --

DR. SOLOMON: Any specific points to

Dr. Chowdhury's question?

DR. SUAREZ-ALMAZOR: No, no.

DR. SOLOMON: I think what you're asking is what characteristics might we be looking for that would --

DR. CHOWDHURY: Two points to summarize the question that I was posing for the committee to think of and give us input is, is the background therapy, now or in the near future, different than what it was in the historical studies? The second point is that, usually, the enrichment criteria in these studies are CRP and based on erosions, and has that changed already or will it change in the near future?

DR. SOLOMON: So any specific comments on that question? Mara? And we'll come back.

DR. BECKER: This is Mara Becker. I don't think the background therapies will be that different yet. I think methotrexate, sulfasalazine, Arava or leflunomide are probably going to be around a long enough time that those non-biologic DMARD background therapies will still

be in use for a while.

But I do think people are more aggressive now than they were, so tolerating a CRP that high without escalating to a biologic therapy that now we have as our options may dwindle those types of patients to be available for comparison, I would suspect.

I think that, now that we have other options beyond the non-biologic DMARDs to use sooner, and we know that, the sooner we get patients under control, the better off their long-term outcomes will be, at least in pediatrics, we're much less willing to accept ongoing inflammation and that damage.

That would be the one thing I could off the top of my head think may pose a problem in the future.

DR. SUAREZ-ALMAZOR: I think the degree of radiographic progression is probably going to be less and less because people are treating earlier, at earlier stages of disease. So I would imagine that they would be included at a lower mean score.

DR. SOLOMON: So just to come back to what the question is at hand for discussion, it's specifically regarding tofacitinib on radiographic progression. I think all these issues are swirling in the background, and I think they underpin some of the analyses that we've looked at.

But to come back to the data at hand, I think the claim that the sponsor is considering is that there's slowing of radiographic progression based on their medication.

Michael? Sorry. And then Maria.

DR. WEISMAN: If the sponsor's claim is that their drug slowed radiographic progression based upon the data that we see at hand, we can't make that conclusion. There has to be some comparison.

As we heard the discussion before about the selection of a margin for a comparison is so critical, and what are the additional factors that go into selecting that margin, which goes back to Dr. Chowdhury's question about historical controls and whether they were as active and progressed at the same rate as the control that you're using now,

is the disease the same, is it going to move in the same direction, that's the challenge.

We expect that to change over time. We expect the ambient nature of our rheumatic diseases that we test the drugs in to be different now than they were 5 or 8 years ago. So that's the challenge. We can't predict the future on it, but we can address those questions.

When you have your discussions with companies about study design, I think you have to bring these issues up because if you live by the sword, you die by the sword. If you have a question now based upon what the data is now, five years hence, things might look different in that population.

DR. SOLOMON: So just to refocus back on the tofacitinib data, I know the sponsor wanted to say a few words.

DR. KANIK: Just a clarification. We're not interested in a claim of slowing or inhibiting structure progression. What I'll point and what the whole purpose of the study was, was that this

information that patients over 12 months did not show differences from that of adalimumab would be useful to practicing physicians.

That's really what we want. We think that it's interesting and useful clinical information, but not that it's, per se, an inhibition of a structural progression claim.

DR. SOLOMON: Yes, Steve?

DR. MEISEL: Steve Meisel. How is that not a claim? I mean, if you say we're not claiming it, but we're going to tell you that there was no difference, wink, wink, nod, nod? Is that how that goes? I'm having a really hard time understanding how that isn't a claim.

DR. KANIK: It's a matter of being in the clinical study section of the label, just having the data there. And I think physicians can make their own determination of that data in the label, but not any specific statement.

DR. MEISEL: Would we be better off having an affirmative statement that says there is no evidence that there is a difference in radiographic

progression?

DR. KANIK: I think that is a discussion we can have with the FDA.

DR. SOLOMON: I'm looking at the FDA. Do you want to help clarify or are you comfortable with what's being said?

DR. CHOWDHURY: I think conceptually we are comfortable with what's being said. I think for the discussion for the exact labeling language, yes, we will have a discussion with the company and sort it out. But I think what we are hearing from the committee telling us, or telling everybody, is useful for us to hear, including your point, is it a claim or is it not?

I think it is very subjective, but generally speaking, if there is information in the product label in a positive way or a negative way is a conclusion that is conveyed to the public.

We look at a statement anywhere in the label as a claim. So that's the context. But I think the point here, as we are hearing from Dr. Brittain and Dr. Weisman, what you actually make of the data

being presented to you is something which is very important for us to hear.

DR. SOLOMON: So I think keeping focused on the data that we observe --

DR. CHOWDHURY: Yes. Thank you.

DR. SOLOMON: Maria?

DR. SUAREZ-ALMAZOR: But again, if the request or what the sponsor would like is to just compare adalimumab with tofacitinib, we are not requesting a non-inferiority margin for ACR20, so why would it be requested for radiological scores? Because for the rest of the outcomes, the primary outcomes, that's not being requested. And I'm assuming that there will be something in the label that says no differences were observed. So why are we using a different benchmark for the radiological scores?

DR. CHOWDHURY: I don't think we are really using a different benchmark. I think I'll have our statistician comment and our colleagues also comment on it.

But the practicality is, for ACR and for

HAQ, we have an outcome measure at approximately month 3. And at up to that point, the society, the community accepts giving placebo is reasonable. And therefore, we can make a conclusion, compared to placebo, whether there is benefit or not.

For the radiographic progression, as Dr. Brittain mentioned, can we look at month 3 and make a conclusion compared to placebo? If you could, one could say that could be enough. But the point generally is for progression of radiographic changes to happen, it takes longer time. And at month 3, you probably would not be able to see a difference between a drug and a placebo. We have to go out for a longer time.

That is the complexity that it brings in how do you do a study. And here, we have a study in hand, and we are asking your opinion.

DR. SOLOMON: We are not going to spend more time talking about what studies should be done. We're going to focus on --

DR. CHOWDHURY: What we haven't had.

DR. SOLOMON: -- what's been done and

whether it's shown us enough that it should be included in the label.

DR. SUAREZ-ALMAZOR: Again, I think it depends on how the label includes the data. But if we are allowing the comparison with adalimumab to move forward without a margin, I'm not sure why the comparison for the radiographic scores cannot be shown or stated without a margin.

DR. LEVIN: Yes. I'll just make two comments. One, just reiterating what Dr. Chowdhury said, we have sufficient data from the placebo comparisons to evaluate whether there is an effect on signs and symptoms without looking at the comparison against adalimumab. But because of the small sample size in the short placebo arm, we don't have sufficient data to make the conclusion about radiographic progression based on a placebo comparison, so we look to see whether we can make a conclusion based on the adalimumab comparison. That's just one clarifying point.

The second is that I just want to clarify or point out that the regulations state that claims,

or implied claims, in labeling should be supported by substantial evidence. I just wanted to point out the implied claims piece of that regulation as well.

DR. SOLOMON: It's all crystal clear now.

(Laughter.)

DR. SOLOMON: James?

DR. CHUNG: Yes. I think there is no definitive conclusions we can draw because of the limitations of the trial design, as we talked about. I think it's important to kind of consider the fact that there was consistent and strong efficacy across multiple domains in this trial. And that combined with the fact that tofacitinib has demonstrated an inhibition of radiographic progression in rheumatoid arthritis, albeit a different disease, but still has that, I think should be considered in terms of the likelihood of what is seen to be true or not. Although, as I said, I think within the confines of this particular study, you can't draw those conclusions.

DR. SOLOMON: Michael?

DR. WEISMAN: I think Greg pointed out to us that our burden here is clear and convincing. It's not weight of the evidence and it's not beyond a reasonable doubt. It's clear and convincing. And that's what I think we need to think about when we judge these questions.

DR. SOLOMON: Jennifer?

DR. HORONJEFF: I agree with those statements. Putting my researcher hat on, I think that it is underpowered to be able to make those claims, but putting my patient hat on, we have to think about the ramifications if you do make those claims.

So let's say my physician prescribes me this, and I see the label or I don't know if they're necessarily talking about direct-to-consumer marketing, but I see a commercial of somebody running through flowers that tells me that I'm going to have help to delay radiographic damage. So I'm thinking, fantastic.

Now, the efficacy looked to be fantastic, so in that sense, I'm feeling good. My signs and

symptoms are reduced. I'm a busy person now because I am able to be active. I am struggling with my insurance. It's hard to get them to cover my images properly, so that's an extra headache. And, frankly, I just don't feel like going to do it because this medication has now said and made a claim that I don't need to be as concerned about it, and I'm feeling good, and it's a hassle to go do.

So that's where I think about the ramifications of if we put this claim there, then we are trying to get them to re-consume their daily activities. And if we're giving them information that tells them they need to stop that or that they don't need to be thinking about some of these other potential conflicts and impairments they could be getting, I'm just really concerned about what that would do without being properly explained. So I just wouldn't make that claim at all.

DR. SOLOMON: Any other discussion regarding the evaluation of the effect of tofacitinib on radiographic progression, psoriatic arthritis?

Again, it's not a necessary consideration when approving the drug, but it is something that may be part of your thinking, and it may be part of the claim, so it's worth us fully discussing. Yes?

DR. CHOWDHURY: Dr. Solomon, I just want to make sure that we have a healthy discussion on that, which I think we did.

DR. SOLOMON: Yes?

DR. CHOWDHURY: The summary that I'm hearing, just to paraphrase, is that this is good information, but not enough for a claim. Am I paraphrasing the discussion or summarizing the discussion correctly?

DR. SOLOMON: That's what I heard, but I'm just chairing this meeting. I think people noted the challenges to the set of analyses. I think that was very crystal clear. I think the importance of the claim was made clear. The challenges with changing background rates was made clear. And I don't think that there was a lot of affirmation that we're confident that we've seen enough evidence to support a claim. But that was

how I heard the input.

DR. CHOWDHURY: Thank you very much.

DR. SOLOMON: So let's move on. Question 2, discuss the safety of tofacitinib for the treatment of adult patients with active psoriatic arthritis.

So this is a broad discussion item. There were a number of adverse events of special interest that we heard about, including serious infection, malignancy, shingles, herpes zoster. There was information about deaths.

Who wants to start off? Dr. Katz?

DR. KATZ: So I would like to put my hat on as rheumatological catastrophizer and ask the committee a question that concerns me, but I'm not an expert in. And in fact the chairperson probably knows more about this than I do.

I want to visit the question of cardiovascular safety in this particular population. We know that psoriatic patients are at increased risk for metabolic syndrome, and we know that shingles puts you at increased risk for cardiovascular adverse events.

So now you have a drug in a patient population that can adversely impact some of these factors. Should the burden of proof of safety by the sponsor in cardiovascular events be held to a higher bar by this committee?

DR. SOLOMON: That's an interesting question. I don't know. What do you think?

DR. KATZ: So I'm acting on the presumption that it should be held to a higher burden of proof of safety, but I don't know that there's data to answer this. Clearly, I would think that it would be within the purview of this committee to suggest to the sponsor that ongoing pharmacovigilance includes specific measurement of these particular issues.

DR. SOLOMON: Yes. I think that's a good point. I think there was mention of a longer-term study going on. In rheumatoid arthritis, there's a several-year follow-up study looking at cardiovascular events. Maybe you can just clarify that for us.

DR. KANIK: Slide MA-94 up on the screen,

please. This is the long-term study on rheumatoid arthritis patients of tofa 5, 10, and adalimumab, and one of the co-primary endpoints is MACE.

DR. SOLOMON: Dr. Katz, this isn't in psoriatics. It's another higher risk population. And I think you alluded to this speculation that shingles may be associated with stroke risk. There's some accumulating evidence supporting that notion, not proven by any stretch.

But I think that part of our discussion here should be obviously about is it safe or is it not safe, but then the safety concerns that linger, how could they be dealt with in ongoing pharmacovigilance and risk mitigation strategies, I think is useful for us to discuss.

Michael?

DR. WEISMAN: I think Dr. Katz brought up a very interesting point, which is, is this particular population more vulnerable to these kind of multiply off-target effects of the JAK inhibitors that we see, and more vulnerable than rheumatoid arthritis patients. I'd like your

opinion on that, too, as a researcher in the area.

The question I have is what happened in the skin psoriasis protocol? Was the reason the FDA letter was given, was it a safety issue or an efficacy issue? What actually happened, and does this have any bearing on our understanding of the safety issue that is brought up now?

DR. CHOWDHURY: I'll take this question. I think, as you heard from Pfizer, there was a submission, and Pfizer subsequently chose to withdraw that application. So I would leave it at that space of confidentiality and not go into it any further.

As far as this discussion for the application in hand, we have displayed, and so has Pfizer, all the safety information on all the patient population, including psoriasis, so relevant information from that program for safety is already in this submission, and we already discussed it.

So I would leave it at that and invite Pfizer if they want to add anything to what I said.

They are saying no, so I think Pfizer is happy with what I said. Thank you very much.

DR. WEISMAN: Dan, what are your thoughts about this special population here, as perhaps being more vulnerable to these multiplicity of target effects that we see in the JAK inhibitors as opposed to a TNF inhibitor, for example?

DR. SOLOMON: Sure. If you are inviting me to opine, I will opine. As you could tell from my line of questioning earlier, clarifying the shingles risk, that to me seems like the clearest signal that Pfizer and others, the consultants for Pfizer, acknowledge clearly. And I think that those may have downstream sequalae that we're still trying to clarify.

So I think the shingles risk is pretty clear. The shingles risk, fortunately for our patients, has the ability to be mitigated with vaccination, as we all know. And we don't really know how well the risk mitigation strategy is working based on what we learned today. There's an impression that it's working, but we don't really

have great data from the sponsor that it's working.

We've all managed these patients. We know what to expect. This is sometimes a very morbid complication, usually not quite so morbid, easy to say as a doc and not as a patient. But I think that the risk mitigation strategy could be much more aggressive than it has been. That's my sense.

I know there's plans, as they said, for a vaccination trial, but it seems like we already have a vaccination that works, that's a little difficult to give because it's a live vaccine, but it seems like there should be a greater effort to make sure that's happening more universally.

As a doc, it's very problematic because of the costs and other issues. And it seems like the sponsor could have a very important role in helping to reduce barriers to getting vaccinated. That's my opinion.

Mara?

DR. BECKER: I actually agree with a number of those points. I think that's great, especially when it comes to herpes zoster. But what I was

going to say was, we have a lot of data here in front of us, and although I love to speculate on what could be or what risks could be in this population, I think that the sponsor has provided us with a large volume of patient data here that we can assess.

At least from my take, I think it's not out of the expectation of what's already been approved for other indications. So in previous reviews and previous approvals, I'd say it's in line with what has been seen in the RA population already. And I just wanted to make that point.

But I agree from a herpes zoster perspective. I do appreciate the responsibility on the sponsor to improve awareness, and consider mitigation strategies, and be more active in that because it's something that is preventable, and I do feel like that responsibility does lie not only on the physician/prescriber, but also on the company who produces it.

DR. MEISEL: Steve Meisel. The point of the vaccination, my understanding is the vaccination is

when you're 60 years old, and a lot of the people with psoriatic arthritis can be a lot younger than that.

DR. SOLOMON: Dr. Winthrop would know this by heart, but I think the recommendations of the people that are on immunosuppressives such as a JAK inhibitor would be indicated for the vaccination. The general population recommendations are people over 60. And this is why we as clinicians have to fight with insurance companies when we have these special populations.

But I think the clear recommendations from the Infectious Disease Society and other folks is that -- I don't know if Dr. Winthrop wants to clarify that for us.

DR. WINTHROP: Thank you. Kevin Winthrop from Portland, Oregon, OHSU. That's correct. The ACIP recommendation for the general population for Zostavax is 60 and up, however, the vaccine is labeled as 50 and up. The ACR recommendation is from 50 and up, and some of the other guideline groups also are consistent with that,

immunosuppressed populations, high-risk populations, to go with the vaccine label, which is age 50 and up.

It certainly doesn't preclude you from using the vaccine in younger individuals. I sometimes do. I know other people do. You may not get it paid for like Dr. Solomon said.

I should also tell you we did a study very recently. Pfizer funded the study and we worked together. We presented at ACR and UR, but we did look at Zostavax, and in fact it's in press presently, so it should be out in the next week or two.

We did look at immunogenicity of that vaccine given prior to starting tofacitinib, and I can just comment on the immunogenicity. It looked very reasonable. Actually, they're putting a slide up here. I guess I can show it. Please put that slide up, SA-119.

On the left side, the column, these are the outcome measures in terms of immunogenicity of the vaccine. So these were patients given the vaccine,

and then two or three weeks later started either tofacitinib or they started placebo. And you can see on the left the IgG, that's the geometric fold rise and IgG titer. And then the second row -- I'm sorry. The third row is ELISPOT measures, which is a cell-mediated immunity measure.

The first row and third row really can just focus on the GMFR. The geometric fold rise was 2.1 in the tofa group for the IgG and 1.7 for the placebo. The confidence intervals overlap. They were similar. And then the ELISPOT measures in the third row, again, slightly higher rise for the tofa, but again, similar with regards to the confidence intervals.

These increases in immune responses post-vaccination are very similar to what we saw in the general shingles prevention trial in the general population. So this is a small study, but I'm encouraged by this, and at least it looks like the vaccine's immunogenic before you start these drugs. And whether you started tofa or placebo in a couple weeks, it didn't seem to matter. They seemed to

have similar immunogenicity.

DR. SOLOMON: So that was a Pfizer-sponsored study to see that the vaccination does work in this population.

DR. WINTHROP: That was a Pfizer trial, yes. Yes. So I'll just say, too, that it's a small study. I certainly agree that they need to do more work to try to understand whether there's a way to prevent zoster.

The last thing I'll mention is, there's a new vaccine coming, too, and that will deserve further evaluation in not just this setting, but across all rheumatology.

DR. SOLOMON: Thank you. Michael, do you want to clarify?

DR. MEISEL: Just looking at the prescribing package insert for Zostavax, it does not give an exception for younger people, so the whole issue of insurance, and indication, and that whole issue that, what gets posed out of that is how long will it last. You get it when you're 30 because of this, and now you're 50 and what do you do then,

that's probably not that elucidated at all.

DR. SOLOMON: Right, still a lot of questions. Michael?

DR. WEISMAN: Just a follow-up to Kevin, are those patients going to be followed for development of zoster, or the endpoint was just the rise in titer on that study?

DR. WINTHROP: Kevin Winthrop, Portland, Oregon. Yes, they are followed, and we did present some preliminary results at the last meeting. There were still several cases of zoster, despite vaccinating. I don't really know what to make of it. There's 52 people in each arm. The placebo group did roll over to tofacitinib, so we essentially had just over 100 people to follow over about 19 months, I think, or 20 months.

So there were several cases despite the vaccine, which isn't surprising necessarily to me.

DR. SOLOMON: Further?

DR. WEISMAN: Are you satisfied, Chair, with the overall Pfizer approach to education and promotion of the concerns for zoster and mitigating

it in this population going forward, or are there still some questions? I think the committee's a little bit uneasy about this, and I'd like to know your thoughts about it.

DR. SOLOMON: Yes. Sure. My sense is that -- again, this is just my opinion -- the sponsor has followed the suggestions of the agency, but I'm not satisfied with either of the suggestions or what's happened, and that's, again, my opinion.

But I think that this is a clear risk, and there are ways to mitigate it. So why we haven't asked for more to be done is unclear to me.

DR. MAYNARD: So this is Janet Maynard from FDA. Just one point of clarification. It would be helpful for FDA, if there are certain things the committee would recommend or think would be helpful to have, recognizing this risk, we would be open to hearing those suggestions or recommended issues that you think should be addressed.

DR. SOLOMON: Thank you. Diane Aronson?

MS. ARONSON: Point of clarification. I

just had a personal experience where I needed to consider the yellow fever vaccination and did a lot of extensive research. But according to the CDC, if you're over 60 and have immune-suppressed drugs, that you should not use this vaccination because there's a probability that you can get the disease and die, one of the complications.

So I'm trying to hear this in relationship to your recommendations of vaccinations and live vaccines. So I'm just confused.

DR. SOLOMON: I'm not sure that I can clarify. I'm looking at Kevin who's looking at me.

(Laughter.)

DR. SOLOMON: I think that yellow fever is a live vaccine. Yes. So I think it's the same set of issues and, maybe, again, a real infectious disease doctor is better than me.

DR. WINTHROP: Yes. That a good question. Kevin Winthrop, Portland, Oregon. I get these referrals personally, and this is an issue with all live vaccines. They really are contraindicated to anyone on a JAK inhibitor or a biologic, so the key

is to try to give them 2 to 4 weeks, probably 4 weeks before starting any of those therapies that you guys use for your patients, except for some of the non-biologic DMARDs where it's been deemed to be safe. So lower-dose prednisone or methotrexate at like 20 and less or 25 milligrams per week and less is thought to be safe.

But a lot of that is expert opinion. There's very little data. And I know when I get consults and people are on the bubble of some of those thresholds, I sometimes shy away and say why don't we wait until you can reduce the dosage on some of those and then get the vaccine.

DR. SOLOMON: Michael?

DR. WEISMAN: I think that the development of JAK inhibitors has spurred vaccine research and created a lot of interesting and important public health concerns about what is going to happen when more and more patients are taking more and more of these medications with target effects that may not be wanted.

So personally, I don't think that the

expertise on this particular committee is sufficient to give you chapter and verse to the FDA about what specific recommendations that you need to discuss with the sponsor going forward about further mitigation of this issue, other than you should have that discussion.

Maybe you should call upon other experts in vaccine research and infectious diseases to provide that expertise to you, and you may have that at the FDA already. You may have that with your colleagues at the NIH. But I feel strongly that you should undertake that process. I don't think we could give you that process specifically now, but you should do it. That's my recommendation.

DR. SOLOMON: Jennifer?

DR. HORONJEFF: Speaking to Dr. Winthrop's point about what their recommendations might be to give a vaccine 4 weeks prior to starting one of these treatments, it makes me think, again, as a patient, that means I have to be off of medication for a month. So do you start to weigh those things out? Do I not want to go on this medication

because I have to come off in order to get a vaccine so that I can go on the medication?

So I'd just think about some of those ramifications and if people will then say, "Well, I'm not going to stop my treatment, and I'll get the vaccination and hope for the best."

In regards to my recommendation for the FDA regarding vaccination and making people aware of these opportunities, how about if somebody is running through flowers, that you could then, as they do that in the commercial, say, "And make sure you talk to your doctor about herpes zoster's vaccinations." So that's my recommendation there.

DR. SOLOMON: I'm seeing the visual right now --

(Laughter.)

DR. SOLOMON: -- the flowers and a shingles rash. I think the risk mitigation strategy is a whole other topic, obviously for a long conversation. Again, it's clear we know how to mitigate this risk, and we know it's a risk.

So what's the standard that we're going to

hold the sponsor to in the risk mitigation strategy? Is it purely education, or is it actually some empiric evidence that the vaccination rates are going up, and how is the sponsor -- what process have they put in place other than CME, which doesn't work, to try to actually change behaviors?

There's decade of literature on this, and I think that just saying we want an educational program is really kind of an abrogation of responsibility.

Why don't we move on to the next question, which is a voting question? So again, I just want to preface it. We did talk a lot about the vaccination and shingles. And just to put that in some context, this is an efficacy vote. So the efficacy conversation was brief. I don't even know if you remember it.

(Laughter.)

DR. SOLOMON: There was really no discussion on signs or symptoms that I could recall other than the data were clear, so there's not much to

summarize there. There was obviously a lot of discussion about the radiographic information and the claim. So I'll read the voting question, and then I think everybody sitting around the table knows how to do the vote. If people are not sure, I can read the instructions again. People know. Okay.

Overall, do the data provide substantial evidence of the efficacy of tofacitinib for the treatment of adult patients with active psoriatic arthritis? And then if not, what further data should be obtained? So I guess the voting can be opened.

(Voting.)

DR. SOLOMON: Do you want to read the results? Thank you.

DR. BAUTISTA: 10 yeses, 1 no, zero abstentions.

DR. SOLOMON: So now the voting is complete. We'll go around the table and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you

did into the record. And we'll start on my right with Erica Brittain.

DR. BRITTAIN: I voted yes. This was an easy vote.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted yes.

DR. WEISMAN: Michael Weisman. I voted yes because I think the sponsor met their burden.

MS. ARONSON: Diane Aronson. I voted no because of, based on this study, concerns about the radiograph progression issue.

DR. HORONJEFF: Jen Horonjeff. I voted yes.

DR. KATZ: James Katz. I voted yes.

DR. BECKER: Mara Becker. I voted yes.

DR. SOLOMON: Dan Solomon. I voted yes. I felt like the sponsor clearly met the requirements.

DR. JONAS: Beth Jonas. I voted yes.

DR. OLIVER: Alyce Oliver. I voted yes. I felt there was sufficient evidence on clinical efficacy, but I don't feel that there's enough evidence for inhibition of radiographic progression.

DR. MEISEL: Steve Meisel. I voted yes.

DR. SOLOMON: So I don't think we're going to -- I think, Diane, you mentioned the data that you would have wanted to have been obtained, and you were the no vote. So I think that that was already stated, so let's go on.

Question 4, another voting question, and again, we did spend a lot of time talking about shingles. There's a whole broad array of safety issues. That's not the only safety issue. It's one particular one, so we want to think about the totality of evidence.

Is this safety profile of tofacitinib adequate to support approval of tofacitinib for the treatment of adult patients with active psoriatic arthritis? And if not, what further data should be obtained? So you can vote.

(Voting.)

DR. SOLOMON: Has everyone voted? Why don't we put the vote tally up?

DR. BAUTISTA: 10 yeses, 1 no, zero abstentions.

DR. SOLOMON: Again, we will go around the room and people can read their vote, their name, their vote, and if they want to give some justification, please do. Erica?

DR. BRITTAIN: Erica Brittain. I voted yes.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted yes.

DR. WEISMAN: Michael Weisman. I voted yes. And the reason is I think that there will be substantial and important discussions with the agency involving risk assessment and strategies going forward, and I welcome that.

MS. ARONSON: Diane Aronson. I voted no. Part of what Dr. Katz mentioned about the vulnerability of the population, and then the demographics in the study were troubling to me, and also the rate of infection.

DR. HORONJEFF: Jen Horonjeff. I voted yes. And although there are safety concerns, I feel like it's nothing different than what we see in other biologics and want to make sure that patients have options.

So although I do hope that there's continued conversation between the sponsor and the FDA on what they can do to make patients aware of these risks and not make claims that aren't true, I still voted yes because I think that it's nothing different than what people on other biologics face.

DR. KATZ: I'm James Katz, and I voted yes.

DR. BECKER: Mara Becker, and I voted yes.

DR. SOLOMON: Dan Solomon. I voted yes. And I see it as a great opportunity for risk mitigation that the sponsor and the agency can take together because we have a clear risk, we have a clear strategy for mitigating the risk, and there's going to be a lot more people exposed to this drug with a known risk, so let's do something about it.

DR. JONAS: Beth Jonas. I voted yes.

DR. OLIVER: Alyce Oliver. I voted yes. I thought that the risk was on par with what we know about tofa and rheumatoid arthritis.

DR. MEISEL: Steve Meisel. I voted yes. I mean, these are nasty drugs, but I think those who use them understand that, and this is no different

than any of the other nasty drugs in these categories.

DR. SOLOMON: Let's move on. So question 5 really asks us to consider the risks and the benefits overall. Do you recommend approval of the proposed dose of tofacitinib for the treatment of adult patients with active psoriatic arthritis?

There's a lot to the question, but we really haven't spent a lot of time talking about dose, I don't think. This is a voting question, so it's not a discussion question unless people really want to discuss further. If not, we can move to a vote.

Please?

DR. MEISEL: Steve Meisel, clarifying actually two questions. We're talking about the 5-milligram BID, not the 11-milligram once-a-day? That's not being requested. Correct?

DR. MAYNARD: Yes. They have requested both the 5-milligram BID and the 11-milligram extended, yes.

DR. MEISEL: They have requested both?

DR. MAYNARD: Correct, yes.

DR. MEISEL: But there has been no data about the 11-milligram once a day?

DR. MAYNARD: So their clinical program was conducted with the 5-milligram twice-a-day immediate-release tablet, and that's what we have focused on, but they have a bridge between that and the 11-milligram.

DR. SOLOMON: Can you explain what a bridge means?

DR. MAYNARD: Sure. In terms of the bridge, they have provided clinical pharmacology information in the past and also have exposure response data that was used to approve that dose for rheumatoid arthritis. And similar arguments have been made for psoriatic arthritis. We'll see if anything else wants to be said about that.

DR. MEISEL: So the agency is confident that the two forms are equivalent enough that they would need to do clinical trials for the 11-milligram?

DR. CHOWDHURY: The answer is yes, and this is something which is pretty common and usually done. When a company would change a formulation,

dosing regimen on some others, sometimes we require clinical data, sometimes, we base it on PK information, and sometimes just in vitro.

So this is a separate process, separate program. For the tofacitinib, that bridge has been established to the satisfaction of the agency, which was previously used for the rheumatoid arthritis program, when there's two dosage forms with two different dosage recommendations already approved.

So that really would apply also here. That's the reason that we didn't bring it up for discussion. But the point is we are comfortable. We have already made the call that these are safe.

DR. MEISEL: The other clarifying question is, in the current package insert, there's a dose reduction of 5 milligrams once a day for people with renal disease. Is that proposed to be carried over for this indication as well?

DR. CHOWDHURY: That is correct, and those are really done with entirely different programs, and those will be also similarly carried forward

for this product.

DR. SOLOMON: Do you have more clarifying questions, Maria?

DR. SUAREZ-ALMAZOR: I was wondering is there a restriction on use of previous DMARDs or anything like that?

DR. MAYNARD: No. So the proposed indication is for the treatment of adult patients with active psoriatic arthritis. So you're correct that there's not that limitation clause as opposed to the rheumatoid arthritis indication, which does have that sort of limitation regarding methotrexate use.

DR. SOLOMON: Michael and then Alyce? Michael and Alyce?

DR. OLIVER: So the drug can be used in monotherapy?

DR. SOLOMON: Yes.

DR. MAYNARD: Pfizer is proposing for use with conventional synthetic DMARDs because that's how it was studied in their clinical program.

DR. SOLOMON: Thank you. That's very

helpful. Any other clarifying points?

(No response.)

DR. SOLOMON: Okay. So we can move to voting.

(Voting.)

DR. SOLOMON: Everyone has voted.

DR. BAUTISTA: 10 yeses, 1 no, zero abstentions.

DR. SOLOMON: Erica Brittain?

DR. BRITTAIN: Erica Brittain. I voted yes for approval. Any risk-benefit standard was clearly met. I will add there did not appear to be evidence to statistically establish the effect of the radiographic progression endpoint, but of course, the study was not designed to demonstrate that statistically.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. Yes.

DR. WEISMAN: Michael Weisman. Yes.

MS. ARONSON: Diane Aronson. No, for the reasons that I mentioned previously for efficacy and safety.

DR. HORONJEFF: Jen Horonjeff. Yes.

DR. KATZ: James Katz. Yes.

DR. BECKER: Mara Becker. Yes.

DR. SOLOMON: Dan Solomon. Yes.

DR. JONAS: Beth Jonas. Yes.

DR. OLIVER: Alyce Oliver. Yes.

DR. MEISEL: Steve Meisel. Unfortunately, there's no yes, but or no if. So my vote is yes, but I want to make sure we are clear that the labeling doesn't have any implied endorsement in terms of the radiological effects.

The other is, I am a bit concerned about general psoriasis. I know that the NDA was withdrawn for that, yet there was a slide in our deck today that we didn't talk much about that talked about the effectiveness of this drug there. I want to make sure that we don't have unintentional leakage of the use of this drug for general arthritis as opposed to psoriatic arthritis -- generalized psoriasis. I'm sorry. I misspoke on that.

Adjournment

DR. SOLOMON: Thank you. I think those are

important points. Before we adjourn, are there any last comments from the FDA?

DR. MAYNARD: I just really wanted to thank the committee for a great discussion today. It was wonderful having your input on the application today. And also, for those of you who were here yesterday, also for the discussion yesterday, so we really thank you for your time and commitment.

(Whereupon, at 12:12 p.m., the meeting was adjourned.)