FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

Monday, April 23, 2018

7:58 a.m. to 4:57 p.m.

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland
Meeting Roster

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**PROCEEDINGS**

**Call to Order**

**Introduction of Committee**

DR. SCHER: Good morning, everyone. Could just get seated. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices. I would also like to identify the FDA press contact, Lauren Smith Dyer. If you're here, please raise your hand. Thank you.

My name is Jose Scher. I am the acting chairperson for the Arthritis Advisory Committee and will be chairing this meeting. I will now call today's Arthritis Advisory Committee meeting to order. We'll start by going around the table and the FDA personnel to my left can take the lead.

DR. THANH HAI: Good morning. I'm Mary Thanh Hai. I'm the deputy director in the Office of Drug Evaluation II.

DR. SEYMOUR: Sally Seymour, acting division director, Division of Pulmonary, Allergy, and Rheumatology Products.
DR. NIKOLOV: Good morning. My name is Nikolay Nikolov. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products.

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

DR. IWATA: Soko Setoguchi from Rutgers University, pharmacoepidemiologist and internist.

DR. ORTEL: Tom Ortel from Duke University. I'm chief of hematology at Duke.

DR. BILKER: Warren Bilker, professor of biostatistics, University of Pennsylvania.

DR. OLIVER: Good morning, Alyce Oliver, Medical College of Georgia. I'm an adult rheumatologist.

DR. WANG: Good morning, Yinhua Wang, designated federal officer.

DR. BOUDREAU: Good morning. I'm Denise Boudreau. I'm from Kaiser Permanente Washington and the University of Washington and I'm a pharmacoepidemiologist.

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

   DR. HORONJEFF: Good morning, Jennifer Horonjeff. I am a juvenile arthritis patient and a consumer representative here today, also a rheumatology researcher at Columbia University and run the patient organization Savvy Cooperative.

   DR. ARONSON: Good morning, Diane Aronson, patient representative.

   DR. BRITTAINE: Erica Brittain. I'm a statistician at National Institutes of Allergy and Infectious Diseases, NIH.

   DR. MILLER: Donald Miller, professor of pharmacy practice at North Dakota State University.

   DR. KIM: Hi. I'm Seoyoung Kim. I'm a rheumatologist and pharmacoepidemiologist at Brigham and Women's Hospital, Harvard Medical School.

   DR. RUSSELL: Jon Russell, retired rheumatologist, San Antonio, Texas.

   DR. CAPLAN: Liron Caplan. I'm a rheumatologist at the Rocky Mountain Regional VA
Medical Center and the University of Colorado and a pharmacoepidemiologist.

DR. CURTIS: Hi, good morning. My name is Sean Curtis. I'm from Merck Research Labs, head of scientific affairs, and I'm the acting industry rep today.

DR. SCHER: Very well. Thank you very much. Just a reminder to mute your mics once you're done speaking. So I will be reading a statement. 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 general reminder, individuals will be allowed to speak into the record only if recognized by the chairperson and we look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory
committee members take care that their conversations about the topics 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. We thank you very much and now I'll pass it to Dr. Yinhua Wang, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. WANG: The Food and Drug Administration is convening today's meeting of the Arthritis Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of 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 the federal ethics and conflict of
interest laws, covered by but not limited to those
found at 18 U.S.C. 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 these committees are in
compliance with the federal ethics and conflict of
interest laws.

Under 18 U.S.C., Section 208, Congress has
authorized FDA to grant waivers to special
government employees and regular federal employees
who have potential financial conflicts when it is
determined that the agency's need for a particular
individual's services outweighs his or her
potential financial conflict of interest or when
the interests 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 discussion of today's
meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves new drug application 207924 for baricitinib tablets, submitted by Eli Lilly and Company for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have an inadequate response or intolerance to methotrexate. The discussion will include the following; efficacy, safety, including the risk of thromboembolic adverse events, dose selection, and overall risk-benefit considerations.

This is a particular matters meeting, during which specific matters related to the Eli Lilly's
NDA 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. Sean Curtis is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Curtis is employed by Merck and Company.

We would like to remind members and temporary voting members that, if the discussion involves any other product or firm not already on the agenda for which the 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. SCHER: We will now have the FDA opening remarks by Dr. Nikolay Nikolov.

**FDA Opening Remarks - Nikolay Nikolov**

DR. NIKOLOV: Good morning, everyone. I would like to welcome you to the Arthritis Advisory Committee meeting for the new drug application or NDA 207924, baricitinib for rheumatoid arthritis. My name is Nikolay Nikolov. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products. I'm also an adult rheumatologist.

Before I begin, I would like to thank the members of the panel for your participation in this Arthritis Advisory Committee meeting. We consider your expert scientific advice and recommendations
very important to our regulatory decision-making processes.

In the next 10 minutes or so, I will provide an overview of the baricitinib development program with emphasis on efficacy, safety, including the risk of thromboembolic adverse events, dose selection, and overall risk-benefit considerations.

The subject of this meeting is the NDA 207924, submitted by Eli Lilly and Company for the new molecular entity, baricitinib, on oral small-molecule inhibitor of Janus kinases being proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

Lilly proposed 2 doses of baricitinib, 2 milligrams and 4 milligrams once daily for oral administration. Specifically, the applicant proposed that the recommended dose is 2 milligrams once daily. For patients with an inadequate response or intolerance to more than 1 DMARD, a dose of 4 milligrams once daily is recommended.
Dose tapering to 2 milligrams once daily will be considered for patients who have achieved sustained control of disease activity with 4 milligrams once daily.

The applicant conducted a large clinical program to evaluate the efficacy and safety of baricitinib. The three phase 2 studies, JADC, JADA, and JADN, summarized in this slide, evaluated doses of baricitinib ranging from 1 milligram to 10 milligrams. While there was some evidence that doses of 1 milligram and higher of baricitinib were efficacious compared to placebo with respect to ACR20 responses in patients with rheumatoid arthritis, Lilly selected to carry forward two doses of baricitinib, 2 milligrams and 4 milligrams, into the phase 3 clinical program.

There were four confirmatory studies in the phase 3 program; JADV, JADX, JADW, and JADZ. Because Lilly targeted 4 milligrams as the to-be-marketed dose, baricitinib, 4 milligrams, was included in all four pivotal trials. But the 2-milligram dose was included in only two of the
phase 3 clinical trials, JADX and JADW. This differential exposure of the 4 milligrams and 2 milligrams dose in the phase 3 program was an important issue that impacted the interpretation of the benefit-risk assessment of the tofacitinib 2-milligram dose, which will be one of the points of discussion of today's meeting.

Studies JADV and JADZ were placebo-controlled studies that also included an active comparator, comparing baricitinib, 4-milligram dose, to adalimumab and methotrexate respectively. Of note, these studies did not include baricitinib, 2-milligram dose, for these comparisons.

Following the completion of the index phase 2 and phase 3 studies, patients were enrolled in the long-term extension study JADY to collect long-term safety information for baricitinib, 2 milligrams and 4 milligrams, doses.

This study included a substudy where patients on baricitinib once daily with low disease activity or remission were randomized to step down to 2-milligram once-daily dose. The data from this
substudy were intended to support the proposed dosing recommendation for dose tapering to 2 milligrams once daily for patients who have achieved sustained control of disease activity with the 4-milligram once-daily dose.

I note that products approved for the treatment of rheumatoid arthritis are approved for chronic use and recommendations like the proposed dose tapering and optimization of therapy represents practice of medicine, which you generally defer to the discretion of the prescriber and, thus, not specified in the product labeling.

Therefore, the FDA's discussion and presentations of the clinical program will primarily focus on the data that supports the benefit-risk assessment of a starting dose of baricitinib in the proposed indication.

The data submitted demonstrated the efficacy of baricitinib in rheumatoid arthritis at doses of 2 milligrams and 4 milligrams once daily for the key domains of signs and symptoms assessed by ACR responses and other measures of clinical response.
and for physical function assessed by HAQ-DI responses.

In studies that included both doses of baricitinib, the data were not consistent in showing a meaningful benefit of 4 milligrams over the 2-milligram dose. Based primarily on integrated efficacy analysis, there is likely a difference between both doses, but that difference if true is likely small.

The data on structural progression assessed by radiographic response show consistent efficacy for the baricitinib 4-milligram dose. However, only one study evaluated the impact of baricitinib, 2 milligrams, on radiographic progression as an exploratory endpoint.

The data from this single trial were not as robust for baricitinib, 2 milligrams, and corroborating evidence from another study was not available.

The applicant has proposed two doses of baricitinib for marketing. Whether there is additional benefits of the 4-milligram dose
compared to the 2-milligram dose of baricitinib is a topic of discussion at today's meeting.

This is important because of the dose-related safety issues identified in the clinical program. The FDA reviewers identified the safety profile of baricitinib consistent with that of a potent immunosuppressant with major safety risks of serious and some fatal infections, including opportunistic infections and tuberculosis, malignancy, laboratory abnormalities of increasing platelet counts, decreasing neutrophil counts, increases in lipid parameters, liver function tests, among others.

Many of these adverse reactions appear to be dose dependent. Additionally, arterial and venous thrombosis were observed in association with baricitinib treatment. While many of the adverse reactions are typical for immunosuppressive therapy used for rheumatoid arthritis, the dose-dependent platelet elevations and reports of thrombotic events are noteworthy.

FDA considered a plausible mechanism related
to JAK inhibition and platelet elevation, as will be discussed later in the FDA presentation.

One of the challenges of the baricitinib clinical program was the assessment of safety. As with other rheumatoid arthritis programs, there was a limited placebo control period and patients could escape and/or cross over to baricitinib higher dose, 4 milligrams. When most of the safety data are from baricitinib treatment groups and there are limited control data, interpretation of imbalances in adverse reactions between treatments is problematic.

In addition, the fact that the baricitinib 2-milligram dose was only included in two of the phase 3 studies limited the assessment of safety of baricitinib, 2-milligram dose. To address some of these limitations, several strategies to combine the safety data were used which will be discussed in further detail in the FDA presentation.

This is important to note when reviewing the safety analyses, as there may be slight differences in events, exposures, rates, and statistics,
depending on the strategy of integrating the safety data. These strategies, however, cannot overcome the limit of placebo-controlled data and limited safety database with the baricitinib 2-milligram dose.

In summary, while the efficacy data are consistent with treatment of baricitinib versus placebo, the results from individual studies were not consistent with a meaningful benefit of 4 milligrams over 2-milligram once-daily dose.

Further, while the data supporting the radiographic response are robust for the baricitinib 4-milligram dose, there is some uncertainty about this effect for the 2-milligram dose, which was studied in only one phase 3 study as an exploratory endpoint. The majority of the safety data are with the higher dose of baricitinib and the identified safety issues raised concerns regarding the 4-milligram dose of baricitinib.

The limited safety database with a lower dose complicated the benefit-risk assessment of the 2-milligram dose of baricitinib. The limited
safety data, database, with a lower dose complicated the benefit-risk assessments of the 2-milligram dose of baricitinib.

Whether the benefit-risk assessment is favorable for the 4- or the 2-milligram dose of baricitinib for the treatment of rheumatoid arthritis is one of the main issues for discussion at today's meeting. To provide further context for the discussion, I will summarize the pertinent regulatory history of the submission.

The original NDA for baricitinib was submitted in January 2016. Due to the submission of new safety information by Lilly late in the review cycle, the PDUFA clock for the NDA review was extended by three months.

Safety concerns were identified, including the risk of thrombosis and the application received a complete response action, meaning not approved in April of 2017 because the overall benefit-risk assessment of baricitinib, 2- and 4-milligram doses was not favorable.

Specific deficiencies included the potential
thrombotic risk, inadequate safety exposure for baricitinib, 2-milligram dose, inability to demonstrate consistent efficacy, advantage of baricitinib 4 over the 2-milligram dose, and a question regarding dose selection, given identified dose-related toxicities.

For transparency, the FDA has included the complete reviews and interpretation of the data from the first review cycle in the briefing document. We note that some of the recommendations and overall conclusions differ between these reviews, reflecting the respective reviewer's interpretation of the data.

These deficiencies, differences in conclusions and benefit-risk assessments highlight the challenges of interpretation of data from this clinical program.

Lilly submitted the response to the complete response action in December of 2017. In the resubmission, the applicant proposed a more narrow indication, specifically treatment of patients with moderately to severely active rheumatoid arthritis.
who have had an inadequate response or are intolerant to methotrexate and the addition of a warning about the potential risk of thrombosis in the warnings and precautions sections in the product labeling.

The resubmission included an update of the accumulated safety information for baricitinib, 2- and 4-milligram doses, in rheumatoid arthritis, including events of deep vein thrombosis and pulmonary embolism.

These analyses were overall consistent with the findings from the first review cycle. The applicant also provided epidemiological data on the incidence of venous thrombosis in the rheumatoid arthritis population and historical data on venous thrombosis for other R.A. therapies with comparisons to the data from the baricitinib program.

The limitations of these comparisons will be discussed further in the FDA presentation. In the resubmission, Lilly also proposed a different dosing strategy for baricitinib, which is more
complicated and deviates from the labeling for other DMARDs products approved for rheumatoid arthritis.

This is also problematic, given that the clinical development program was not designed to support the proposed dosing strategy. The submitted rationale for the dosing recommendation is primarily based on post hoc analyses which do not provide convincing evidence that the 4-milligram dose provides meaningful added benefit over 2 milligram in the proposed subpopulation of patients with an inadequate response or intolerance to 2 or more DMARDs.

This will be discussed in further detail during the FDA presentation. Therefore, to avoid being distracted with nuances of the proposed dosage administration of baricitinib, we ask the advisory committee members to consider the benefit-risk assessment of each proposed dose of baricitinib for the principal indication, which is the treatment of adult patients with rheumatoid arthritis who have had an inadequate response or
intolerance to methotrexate, as detailed in the
points for discussion and voting questions in the
next few slides.

The first discussion point refers to the
efficacy data of baricitinib for the treatment of
adult patients with moderately to severely active
rheumatoid arthritis who have had an inadequate
response or intolerance to methotrexate. We would
like to obtain the committee's input on what
available data support a benefit of one dose over
the other. This will be followed by a separate
voting on the efficacy for each of the proposed
doses.

The next discussion point relates to the
safety of baricitinib in the proposed indication,
where we would like to seek the committee's input
on the adequacy of the safety database for the
2-milligram dose of baricitinib, the adverse events
of special interest, and whether the safety data
are more favorable for one dose over the other.

This will be followed by a separate voting
question on the safety of each of the proposed
doses. Then we will conclude with separate voting on the overall benefit-risk profile to support approval for each of the proposed two doses in the proposed indication. Thank you for your attention. I will turn the podium back to you, Dr. Scher.

DR. SCHER: Thank you very much. So now is the time for the applicant presentation. Yes, sorry. I was reminded that Dr. Katz just joined us, so if you can, introduce yourself to the audience.

DR. KATZ: I'm James Katz. I'm the rheumatology fellowship program director at the NIH.

DR. SCHER: Thank you very much. Both the FDA and the public believe in a transparent process for both 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 sponsor'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 presentations, it will not preclude you from speaking.

We will now proceed with Eli Lilly's presentation. Thank you.

Applicant Presentation – Robin Wojcieszek

DR. WOJCIESZEK: Good morning. I'm Robin Wojcieszek, senior director of regulatory affairs at Lilly. I want to thank the FDA and members of this advisory committee for participating in today's meeting.

We are pleased to present data supporting
the approval of baricitinib for the treatment of rheumatoid arthritis. Baricitinib will provide a needed treatment option for you as patients, who have struggled to manage their moderate to severe rheumatoid arthritis with current therapies.

Today, the greatest need in rheumatoid arthritis is an effective treatment for patients who have tried available therapies but continue to have persistent active disease with associated pain, disability, irreversible joint damage, and the risk of early mortality.

Unfortunately, many patients are inadequately treated with current therapies. Up to 75 to 90 percent of patients do not achieve the treatment target of remission. That's why Lilly and Incyte co-developed baricitinib.

Baricitinib is a small molecule that works inside the cell by inhibiting the activity of Janus Kinase enzymes with selectivity for JAK1 and JAK2. An oral once-daily tablet, baricitinib reduces inflammation by modulating the JAK-STAT pathway and disrupts the signaling of multiple pro-inflammatory
cytokines involved in RA pathogenesis.

The baricitinib clinical program studied patients across the RA continuum from those who are treatment naïve to those who are highly treatment refractory. The whole program included 27 studies, which I've outlined here, including the long-term extension study.

For today's presentation, our primary dataset will focus on the efficacy results of our four pivotal phase 3 studies that enrolled a total of 3,100 patients. Each study met its primary endpoint. Our safety presentation includes the data from our completed and ongoing RA studies.

Let me now turn to the regulatory pathway that led us to this important meeting. Global marketing applications for baricitinib were submitted to regulatory authorities in 2016, with the first submission to FDA in January. The applications included both the 4- and 2-milligram doses. To date, more than 40 countries have approved both the 2-milligram and 4-milligram doses of baricitinib, including E.U. approval in February.
of 2017 followed by Japan.

In April of last year, FDA sent Lilly a complete response letter. Based on that initial submission, the complete response noted inconsistent efficacy advantages of the 4-milligram over the 2-milligram and suggested the need to evaluate lower doses due to identified dose-related adverse events.

The complete response also indicated there were inadequate 2-milligram safety exposures for conducting a full risk assessment of that dose. The primary safety concern was the potential for venous thrombotic risk due to the imbalance of events that occurred during the placebo-controlled period with the 4-milligram compared to both the 2-milligram and placebo.

As such, with questions about consistent efficacy, dose-related adverse events, and the potential risk of thrombotic events, the complete response stated an inability to conclude that there was a favorable benefit-risk profile for baricitinib.
In response, Lilly and FDA agree to the contents of a resubmission which we believe addressed the identified issues and set the stage for our discussion today.

It includes an updated RA safety database with 7,860 patient-years of exposures, including an increase in 2-milligram exposures to 1,275 patient-years. Altogether, this is a nearly 90 percent increase in patient-years of exposures since the initial submission. Importantly, this additional data did not identify a new safety signal and it increased the precision of the risk assessments.

Our resubmission evaluates the safety profile of baricitinib in the context of other approved RA treatments, including the potential thrombotic risk. The resubmission also includes a proposed risk management plan as well as new efficacy analyses to support the consistent added benefit of 4 milligrams for some but not all patients.

The resubmission also includes, in response to FDA's concerns, proposed dosing. Here is our
proposed indication. Baricitinib is for the
treatment of adult patients with moderately to
severely active rheumatoid arthritis who had an
inadequate response or intolerance to methotrexate.

Within the indicated population, baricitinib
can address the patients' needs across the RA
continuum. Having both doses available provides
the flexibility for physicians to meet patients
where they are on this continuum. And we look
forward to working with the agency to determine a
dosing recommendation that best meets patients'
needs.

For example, some patients with more
treatment-refractory disease need the 4-milligram
dose in order to effectively manage their disease.
Others will be very successful on 2 milligrams.

The discussion questions posed by FDA for
today's meeting include the benefit-risk of each
dose, questions which typically serve as the basis
for approval. Baricitinib will present data to
support the benefit and risk of the 2-milligram
dose and the benefit-risk of the 4-milligram dose.
In addition to address concerns raised by the agency, we will also include benefit and risk comparisons between the 2-milligram and 4-milligram doses. And we’ll evaluate baricitinib relative to approved RA therapies. While these comparisons are not the primary basis for approval, we agree that they can provide important context to determine an acceptable level of risk for a given benefit.

I would now like to turn to our agenda. Dr. Mark Genovese will discuss current unmet needs in treating RA. Dr. Terence Rooney will describe our clinical program and review the efficacy data. Dr. Melissa Veenhuizen will present our safety data. Dr. Josef Smolen will provide a clinical perspective of baricitinib as an RA therapy. And Dr. James McGill will conclude our presentation and moderate the Q&A.

We also have additional experts with us today. All outside experts have been compensated for their time and travel to today's meeting. Thank you. I'll now turn the lectern over to Dr. Mark Genovese.
Applicant Presentation - Mark Genovese

DR. GENOVESE: Good morning. I'm Mark Genovese and I'm the director of the rheumatology clinic in the Division of Immunology and Rheumatology at Stanford University.

I was the principal investigator in the JADW, the RA-BEACON study, looking at the effects of baricitinib in patients with an inadequate response to biological DMARDs. I've been a practicing rheumatologist and an active clinical trial investigator for over 20 years.

It remains an unmet need for patients to have effective therapies for those patients who have already tried available therapies, but continue to have persistent, active disease which is associated with pain, disability, joint damage, and accelerated mortality.

Now, rheumatoid arthritis is a chronic, progressive, inflammatory, autoimmune disease. Patients with moderately to severely active disease experience systemic inflammation, contributing to a constellation of symptoms that can result in
significant restrictions in daily living.

Patients frequently report pain, fatigue, and functional impairment in work, and with leisure activities. The disease affects approximately 1.3 million people in the United States and approximately three-quarters of these are women.

While it can present at any age, the average age of onset is 55 years, the time when most are still expecting to live very active and productive lives. The disease itself affects patients' daily function and quality of life, particularly to an extent that has been shown to be comparable or worse than patients with type 2 diabetes and cardiovascular disease.

There's also an associated higher rate of mortality. High disease activity is associated with the loss of approximately 10 years of life. And cardiovascular disease is the most prevalent morbidity and the leading cause of death in patients with rheumatoid arthritis.

Serious infections are also a significant co-morbidity. Malignancies such as lymphomas and
lung cancer are also reported more frequently than in the general population. These events have been seen in the clinical programs for all approved RA therapies.

Now, the current treatment goals are to achieve disease remission or low disease activity in every patient. We look to stop or reduce inflammation, prevent joint damage and organ damage, relieve pain, improve physical function, and reduce long-term complications.

It's important to treat effectively and routinely to the status of patients. If there are no improvements seen within three months or the treatment target has not been reached by six months, we modify therapy in order to achieve the treatment goals.

Now, we currently have a number of medications available to help achieve these goals. Most important is to start early and to continue to adjust therapy by treating to a target. Upon diagnosis, we generally start with a conventional, synthetic, disease-modifying drug, or DMARD such as
Depending on the patient response, we use methotrexate as a monotherapy or in combination with other DMARDs. If a patient fails to achieve an adequate response or stops responding, we begin a biologic DMARD, usually a TNF-alpha inhibitor, commonly used in combination with background methotrexate.

Other biologic mechanisms of action or JAK inhibitors are also options. Patients who fail a biologic DMARD or JAK inhibitor are often switched to another option. If they achieve a sustained remission, both the American College of Rheumatology and the European League Against Rheumatism recommend considering dose tapering, but not discontinuation of therapies.

Now, to better understand the extent of the unmet need, let's look at the ACR 70 responses identified in clinical trials of patients who have had inadequate response to methotrexate. Note that the ACR 70 can be used as a proxy for remission.

While not directly comparable, these data
are taken from a series of RA clinical trials that provide a broad overview of the probability of achieving an ACR 70 response. For each study, the column on the left represents placebo in combination with background methotrexate and the column on the right is a combination of a particular therapeutic agent plus methotrexate.

As you can see, despite our successes, there's room for improvement. When current biologics are taken in combination with methotrexate, only a minority of the methotrexate inadequate responders actually achieve an ACR 70.

If we look at the growing population of patients who have had an inadequate response to previous biologics, the results are actually even worse. The chances of achieving an ACR 70 are quite low, including with the most recently approved therapies, including tofacitinib and sarilumab.

Up to 90 percent of patients do not reach treatment targets with currently available therapies. Additionally, patients may encounter
safety issues that rheumatologists are accustomed
to diagnosing and managing. It may include serious
infections, amine reactions, malignancy, and
laboratory changes such as liver function
parameters, blood cell counts, and lipids.

Now, despite the advent of new therapies
over the past 20 years, we still have an unmet need
for patients who are unable to achieve an adequate
response or have an intolerability to current
therapies.

Even with the introduction of biologics,
only a minority of patients are achieving a true
remission. Many will have a partial response or
they may lose efficacy over time. Others do not
tolerate treatment or may experience a side effect.

While a cure remains elusive, we want all
patients who have RA to have an opportunity to
reduce their symptoms, improve physical function,
and improve quality of life. Patients need options
that increase their chances for disease control
over current standards of care and help them
promptly attain and maintain their treatment goals.
Thank you. I'm pleased to invite Dr. Terence Rooney to present evidence supporting baricitinib's therapeutic benefit.

**Applicant Presentation – Terence Rooney**

DR. ROONEY: Thank you. Good morning. My name is Terence Rooney and I'll be presenting the efficacy results of the baricitinib clinical program. I'm a senior medical director at Lilly and I've had responsibility for clinical development of baricitinib since 2012.

My background includes more than 10 years in clinical care and research for patients with RA as a practicing rheumatologist and as an internal medicine physician.

The baricitinib RA program included four positive pivotal trials. They showed that baricitinib, 2 and 4 milligrams, were superior to placebo and that 4 milligrams was superior to standards of care. That's oral methotrexate and injectable adalimumab.

So the findings demonstrated that, with baricitinib, patients could rapidly attain and
maintain their treatment goals. A dose taper study then showed the patients who did achieve sustained disease control at the 4-milligram dose, could maintain it after tapering to 2 milligrams or they could recapture control with return to 4 if they needed.

So we propose for your consideration that the data support a valuable role for both the 2- and 4-milligram daily doses in RA therapy as we'll show. And some patients will need 4 milligrams to control their disease.

This includes those with more treatment-refractory RA, where unmet need is greatest. For many patients, 2 milligrams will be effective either as initial dose or for long-term maintenance after induction of disease control with 4 milligrams.

Providing the option to use both doses can allow patients to realize the full potential for benefit that baricitinib has to offer. So let's review the data that supports this summary.

In phase 2, we explored a dose range of
baricitinib, 1 to 10 milligrams a day, versus placebo. All the doses were biologically active, with 4 milligrams daily showing the most rapid, large, and consistent effects.

The higher doses didn't show added benefit and efficacy was less consistent as the dose decreased. Now, the upcoming figures will show you the estimated exposure response relationship from phase 2.

They plot plasma drug concentration on the X axis against achieving low disease activity, which is a target of therapy, on the Y axis. So for 4 milligrams, the drug concentrations resided to the right of the shoulder on the flat region of the curve, where patients have the best chance of response.

For 2 milligrams, the exposures were somewhat lower on the curve, where efficacy starts to decrease. And the 1-milligram concentrations encompass the steep part of the curve, where many patients won't respond.

So these observations led us to take 2 and 4
milligrams into phase 3. 4 milligrams was most likely to offer patients the best response and differentiate not only from placebo, but also from active therapies. Two milligrams provided a lower dose option that could be appropriate for some patients.

The data didn't support further development of the 1-milligram dose because it wouldn't offer clinically meaningful efficacy for most patients. And FDA agreed with Lilly's plan to carry these two doses into phase 3.

The phase 3 program enrolled patients with moderately to severely active RA at all points along the treatment continuum. Two trials compared 2 and 4 milligrams to placebo; one in patients who previously failed an injectable biologic and one in patients who failed oral conventional DMARDs but hadn't yet tried a biologic.

Then two trials compared baricitinib to active comparators, representing standards of care. The first compared against oral methotrexate in the DMARD-naïve population and the second compared
against adalimumab, an injectable biologic. That trial also included a placebo control and note that, in line with current ethical norms and with FDA guidance, the placebo exposure was limited across the program, here to a maximum of 24 weeks.

So taken together, the four trials provided a comprehensive assessment of baricitinib in the context of existing RA therapies. We'll also review results from an ongoing long-term extension study that enrolled patients who completed these four trials.

Now, our efficacy endpoints covered the four key domains in RA treatment. That's signs and symptoms, physical function or disability, patient-reported outcomes or PROs, and radiographic progression of structural joint damage.

The primary outcome measure in all the studies was the ACR20 response. That's where responders must show at least a 20 percent improvement from baseline across a core set of components. And this is the traditional endpoint for RA registration trials.
ACR50 and ACR70 responses then define patients having higher, 50 and 70 percent, levels of improvement. And they were additional secondary measures.

Now, other composite disease activity scores included the Disease Activity Score or DAS28, the Simplified Disease Activity Index or SDAI, and the Clinical Disease Activity Index or CDAI, and they were used as key and secondary objectives across the program.

Those measures can define low disease activity and remission, which are the recommended clinical treatment targets. Also, FDA and ACR publications note that those continues measures can be more sensitive for discriminating dose response than dichotomous ACR responses.

The key objectives of each study also included change from baseline in the HAQ disability questionnaire. As Dr. Genovese noted, relieving patient-reported symptoms is a valued treatment goal. And so we included patient electronic daily diaries that assess worst pain, morning joint
stiffness, and tiredness in two of the studies.

Finally, then, the modified Total Sharp Score or mTSS measures radiographic joint damage. And that was a key secondary measure in the two active comparator trials and it was exploratory in another study. And slowing joint damage is the quality that designs a treatment as disease modifying.

Now, as I review the phase 3 efficacy for you, unless otherwise stated, any results would be from pre-specified analyses. And for your clarity, I'll note where any post hoc analyses are shared.

So let's begin with the two studies that evaluated baricitinib, 2 and 4 milligrams, showing superiority for each dose to placebo. That's studies JADW and JADX. The two studies used similar designs. Patients were randomized to receive 24 weeks of treatment with placebo, baricitinib, 2 milligrams, or baricitinib, 4 milligrams.

The primary endpoint is measured at week 12 and, at week 16 or later, patients with inadequate
response could be rescued to open-label baricitinib, 4 milligrams. And as for all the studies, rescued patients were then defined as non-responders and they stayed blind to their initial treatment assignment.

The key difference between the two trials was the population. JADW enrolled 527 patients with inadequate response or intolerance to one or more prior biologics, including at least one TNF inhibitor. JADX enrolled 684 patients with inadequate response or intolerance to one or more oral conventional DMARDs, but who had never received a biologic.

So let's first look at the results for JADW. That's in the most treatment-resistant RA patients. Now, compared to prior anti-TNF failure studies, JADW included a uniquely high proportion of patients, some 40 percent, who had failed multiple classes of biologic. The primary objective was met. 4 milligrams was superior to placebo based on ACR20 and that's shown in green.

As we advance, colored fills will appear for
the results of key objectives that were included in the multiplicity control plan.

So 4 milligrams was also superior to placebo and the key objectives for improving disease activity and physical function. SDAI remission in orange wasn't significant for 4 milligrams versus placebo at week 12. And this is an ambitious target for such a refractory group, especially after only 12 weeks.

Now, key endpoints for the 2-milligram dose showed the same pattern. Since objectives for 4 milligrams were tested first in the multiplicity arrangement and the test for SDAI remission was non-significant, the comparisons of 2 milligrams versus placebo, including those shown in the lighter green, weren't evaluated with multiplicity control.

Nonetheless, though, the results did indicate that 2 milligrams is an effective dose. For most measures, 4 milligrams had the largest effects for these highly treatment-refractory patients. Now, as I noted earlier, dose response
can be most clearly observed using continuous
disease activity measures.

So here is mean change from baseline in
DAS28 and SDAI at all of the study visits. The 2-
milligram dose in the gold showed significant
improvements over placebo from as early as week 1.
At all the time points, the 4-milligram dose in the
blue produced improvements at least 1.5 times large
as the 2-milligram treatment effect.

Now, as the dotted line shows here, by 4
weeks, improvement with 4 milligrams was already as
large as 2 milligrams ever showed during the full
six months. Now, development programs in RA aren't
designed to test for statistical significance
between active doses in individual studies.

However, the improvements in disease
activity were significantly larger for 4 than 2
milligrams throughout this study and that's shown
here as plus symbols. And we provide you this last
post-hoc finding to reflect the between-dose
significance testing explored in FDA's briefing
book.
We also assessed achievement of treatment targets and we saw a similar pattern. So here are SDAI remission and low disease activity rates. Only 4 milligrams significantly improved the stringent remission rate versus placebo.

Now, in fairness for these patients, low disease activity or better might be a more realistic goal and that's recognized in treat-to-target guidelines. And both doses significantly improved that versus placebo.

So by week 24, the difference between 2 milligrams at 22 percent and placebo at 14 percent would indicate a number needed to treat or NNT of 12 or 13 patients to bring one to low disease activity. For 4 milligrams versus placebo, the corresponding NNT would be about 6.

So while both doses of baricitinib were efficacious in JADW, for optimal efficacy, these biologic refractory patients ended 4 milligrams a day.

Now, let's look at the second study showing superiority of the 2- and 4-milligram doses to
placebo. So study JADX studied patients who had
failed conventional DMARDs, but not biologics.
More than half had failed 2 or more conventional
DMARDs. The primary objective was again met.
ACR20 rates were higher for 4 milligrams versus
placebo and, in fact, all key objectives were met.

Both doses were superior to placebo on all
of the efficacy endpoints shown here. Now, in this population, dose response was less evident than in
the prior study, JADW. Several outcomes,
especially categorical measures, didn't show an
advantage for the higher dose at week 12.

So let's examine again the continuous
composite disease activity scores which are
sensitive for comparing between doses. Both doses showed rapid and significant improvement in disease activity. We do see a conventional dose response pattern, but it's less marked than the highly
treatment-refractory patients from study JADW.

Here, the improvement in disease activity
was closer for 2 and 4 milligrams. So the dose
response patterns seen between these first two
phase 3 studies aligned with the idea that
different patients can need different levels of
treatment to achieve a given response in this case,
depending on how treatment refractory their disease
had proven to be.

So within study JADX, stratifying patients
based on their history of failed DMARD treatments
was consistent with this. So in this post hoc
analysis, looking across all of the study time
points, there's little difference between the doses
in less refractory patients while more refractory
patients showed a greater need for 4 milligrams.
And as in JADW, the between-dose differences here
were statistically significant over time and that's
shown by the plus signs.

Significant interaction tests supported that
observation. Now, in JADX, both doses also
significantly inhibited radiographic progression of
statistical joint damage versus placebo and that's
shown here as mean change from baseline in mTSS
week 24.

The treatment effect for the 4-milligram
group remains significant versus placebo in additional analyses that used more conservative statistical methods. So these first two placebo-controlled trials showed that the 2- and 4-milligram doses were superior to placebo across important domains of efficacy.

Some patients needed 4 milligrams, including those with more refractory disease. For others, 2 milligrams was a good choice. An exploratory PK/PD analysis supports this. So here, you'll see EC80; in other words, the drug concentration that patients need to derive 80 percent of the maximum improvement the baricitinib can produce for DAS28 CRP at week 12.

Single conventional DMARD inadequate responders need lower baricitinib concentrations than those patients with more previous treatment failures, whether that's to multiple conventional DMARDs or to biologics.

For those patients more resistant to RA, only the 4-milligram exposure range in blue color reaches EC80. For single DMARD inadequate
responders, either dose can do so. Let's now look at the two studies where baricitinib, 4 milligrams, showed superior efficacy to current standards of care, methotrexate and adalimumab.

We'll begin with the methotrexate comparison, with study JADZ. This trial compared baricitinib, 4 milligrams, to oral in methotrexate in patients who were DMARD naïve. 584 patients were randomized to a year of treatment with methotrexate, baricitinib, 4 milligrams, or the combination of the two.

The primary objective was met. 4 milligrams was superior to methotrexate based on ACR20 at week 24. And in fact, whether it was given alone or in combination with methotrexate, baricitinib was superior to methotrexate on all the key endpoints at week 24 except radiographic progression, where only the combination group showed superiority.

Now, let's look at JADV. That was the largest of the completed phase 3 studies. This study enrolled patients with inadequate response to methotrexate. They were naïve to biologics, but
they may have failed other conventional DMARDs.
And as for study JADX, more than half had failed 2 or more conventional DMARDs.

Thirteen hundred and five patients received baricitinib, 4 milligrams, adalimumab or biologic or placebo, and we used a double dummy approach to maintain the blind. The active treatments lasted for 52 weeks and placebo lasted up to 24 weeks before then switching to baricitinib if those patients hadn't already been rescued at or after week 16.

All the patients continued their stable background methotrexate and this was to allow for optimal efficacy of adalimumab.

The primary objective was met. Baricitinib, 4 milligrams, was superior to placebo based on ACR20. It was also superior to placebo on all of the other key objectives. That's disease activity, remission, physical function, other patient-reported outcomes, and radiographic progression.

Now, two comparisons of baricitinib to adalimumab were pre-specified key objectives; that
is, with strong control for multiplicity, ACR20, and change from baseline in DAS28 at week 12.

Baricitinib showed statistically significant improvement over adalimumab for both endpoints. In fact, it was superior to the biologic based on almost all additional clinical objectives, including every composite score, all the ACR components, physical function, which is typically a difficult measure to show differences between active treatments, and other PROs.

So here are DAS28 and SDAI disease activity scores. Both the active treatments were superior to placebo and that's shown by the asterisks. But baricitinib is superior to adalimumab from the earliest weeks through the full year of treatment, as you can see from the plus signs.

Here are the patient-reported daily electronic diary outcomes. That's symptoms of high relevance in patients' daily lives. Again, both active treatments showed benefit over placebo, but with significantly greater improvements for baricitinib compared to adalimumab across each
domain. That includes duration and severity of morning joint stiffness, joint pain, and tiredness.

Per the bottom left panel, by week 12, baricitinib reduced pain more than twice as much as adalimumab. The last set of results I'll share are from the long-term extension study. That's JADY. And it receives patients from all of the phase 3 studies.

So in addition to confirming long-term safety and efficacy, JADY assesses the ability to taper the dose of baricitinib after achieving sustained disease control. And that's a strategy that's recommended for consideration in professional guidelines, as shared earlier by Dr. Genovese.

So patients who had received baricitinib, 4 milligrams, for at least 15 months and achieved sustained low disease activity or remission were randomized to continue on baricitinib, 4 milligrams, or taper to 2 milligrams with dose blinding and without revealing that randomization had occurred.
Now, Clinical Disease activity Index or CDAI was the principal outcome measure. This close relative of SDAI is well accepted and validated and it requires no lab results to calculate. So that permits on-the-spot determination of disease status at the study visits.

Eight hundred and seventy-four DMARD-IR patients who were in sustained low disease activity or remission on 4 milligrams were enrolled and randomized. Here, you'll see the proportions who were still in those disease control categories through the subsequent 48 weeks.

So we continued 4 milligrams compared to 2 milligrams dose taper. Significantly more patients maintained remission -- that's the bars here -- or low disease activity, the tall bars. This was supported by multiple other pre-specified analyses and they included change in the disease activity scores and their components and the time to relapse.

Importantly, though, and supporting the reasonableness of this treatment strategy, most
patients who tapered to 2 could maintain their disease control. So that's shown by the full height of the gold bars. Fewer than 1 in 5 needed rescue after a 2-milligram dose taper and those who did could recapture control with return to 4 milligrams if they needed.

So to recap, the baricitinib phase 3 program included 4 positive phase 3 studies across the spectrum of RA care from patients who were treatment naïve to those who had failed multiple prior therapies.

As you've heard or read from both FDA and Lilly, significant benefit was demonstrated in all the important domains of efficacy. This was shown for baricitinib, 2 and 4 milligrams, versus placebo and for 4 milligrams versus oral and injectable standards of care.

To our knowledge, this was the first time any RA therapy showed superior efficacy to a biologic TNF inhibitor used with background methotrexate with strong statistical control for multiplicity.
In patients for whom sustained disease control was induced, a large, randomized blinded study provides robust evidence to inform considering taper to a lower dose for maintenance. This has been advocated in professional guidelines for some time, but to our knowledge, this was also a first for an RA registration program.

We propose that the results of these studies support a valuable role in RA care for both the 2- and 4-milligram doses. An important unmet need remains for patients who can't reach their goals despite trying multiple prior therapies.

For their more difficult-to-treat RA, these patients need the 4-milligram dose for optimal results. For many patients, 2 milligrams will be suitable. That can include those with less difficult-to-treat disease for improvements in disease activity, more comparable for 2 and 4 milligrams or patients who achieve disease control with 4 milligrams who can then explore long-term maintenance with the lower dose.

Having both of these effective dose options
can allow U.S. physicians to flexibly tailor this novel treatment in a way that helps them meet their patients' needs according to their individual circumstances. And this is another core principle of RA care, as outlined in treatment guidelines.

Thank you very much for your attention and for your consideration. I'll now invite Dr. Veenhuizen to discuss safety.

**Applicant Presentation – Melissa Veenhuizen**

**DR. VEENHUIZEN:** Good morning. I'm Melissa Veenhuizen and I've worked in drug safety assessment for more than 15 years. I'm responsible for the medical team characterizing the safety of Lilly medicines developed for pain and autoimmune diseases.

Today, I'll be presenting the safety results for baricitinib. First, I'll describe the safety exposures for the baricitinib RA development program followed by an overview of the safety results, including infection, malignancy, major adverse cardiovascular events or MACE, laboratory changes, and thrombotic events.
I'll then discuss risk management plans and post-approval safety data from countries where baricitinib is approved. The baricitinib RA safety database is substantial. At initial submission, we had 3,464 RA patients with a total of 4,214 patient-years of exposure. In the resubmission, 3,492 RA patients have received baricitinib at any dose with 7,860 patient-years of exposure, a nearly 90 percent increase.

Now, 1,005 patients have been exposed to the 2-milligram dose with 1,275 patient-years of exposure. And 3,107 patients have received a 4-milligram dose for 6,392 patient-years of exposure.

This integrated safety database will be the focus of my presentation. I'll be showing results from three safety datasets. The first comprises placebo-controlled data from the four studies where both the 2- and 4-milligram were evaluated. This dataset allows a direct comparison of the two doses against placebo and is a useful way to look for a short-term dose response.

As this is a short time period, we included
the extended dataset containing the 7 studies that evaluated either the 2- or 4-milligram dose. It includes long-term extension data, following patients that continue beyond the placebo-controlled time period until dose switch or rescue.

The number of patients and duration of exposure is increased, facilitating evaluation by dose for events that may be uncommon or have a delayed onset. Finally, the all bari RA dataset includes all baricitinib exposures and is the largest. It provides the most precise estimate of adverse event incidence rates and helps identify events that may emerge after long-term exposure.

Let's begin with an overview of safety. Shown here is the frequency of treatment-emergent adverse events or TEAEs, serious adverse events or SAEs, and adverse events leading to permanent discontinuation in the placebo-controlled period.

The difference between the baricitinib and placebo or between baricitinib doses for SAEs and discontinuations were small. A total of 3 deaths were reported, 1 with 4-milligram baricitinib or
0.2 percent and 2 with placebo at 0.4 percent. All SAEs presented are according to ICH and 21 C.F.R. criteria. Next, we'll review the incidence rates in the all bari RA and extended datasets beginning with deaths and SAEs.

On the Y axis is the incidence rate per 100 patient-years and under the x axis is the dataset, the number of patients, and the patient-years of exposure supporting each data point, including follow-up events and time. The incidence rate of death is 0.35 in the all bari RA dataset.

The incidence rate was 0.16 for 2-milligram and 0.34 for 4-milligram treated patients. The low number of deaths limits our ability to make meaningful comparisons. However, these incidence rates are within the range reported from other RA clinical development programs based on FDA summaries at the time of submission for abatacept, tocilizumab, adalimumab, and tofacitinib.

Serious adverse events occurred at an incidence rate of 8.9 in the all bari RA group with rates of 10.1 and 9.2 for the 2-milligram and 4-
milligram treated patients. Note these rates are within the range reported from other RA clinical programs.

As with other RA therapies, infections were an adverse event of special interest. They were frequently reported and most were non-serious. In the placebo-controlled period, a similar frequency of serious infection was noted between placebo and baricitinib, 2 milligram, at 1 percent with frequency of 2 percent for 4 milligram.

Pneumonia and herpes zoster were the most common serious infections. And overall, 1 to 2 percent of baricitinib-treated patients discontinued due to an infection. The incidence rate of serious infection was 3.0 per 100 patient-years for the all bari RA group with an incidence rate of 3.3 for 2-milligram and 3.2 for 4-milligram patients.

These rates are, again, within the range reported for other RA therapies, as shown here.
monodermatomal and mild to moderate. There were no cases of visceral disease or death due to zoster.

From the all bari RA group, the zoster incidence rate was 3.3, with rates of 2.8 and 3.3 for the 2- and 4-milligram group. These baricitinib rates are between those of tocilizumab and tofacitinib. And herpes zoster is recognized as an adverse drug reaction in baricitinib global labeling.

Relative to opportunistic infection, 11 cases of clinical TB were reported in the all bari dataset for an incidence rate of 0.14. All were from endemic regions. One additional case of clinical TB was reported after the April 2017 data cut from a U.S. patient with a previous history of latent TB.

Multidermatomal herpes zoster was reported at an incidence rate of 0.28 for the all bari RA group with no events at 2 milligram and an incidence rate of 0.27 for 4 milligram. Other opportunistic infections were infrequent with an incidence rate of 0.3 for the all bari RA, 2-
milligram and 4-milligram dose groups.

These opportunistic infections are based on
the FDA-aligned case definitions and the number of
events are shown for the infections listed.

We also carefully evaluated malignancies.
The overall incidence rate for the all bari RA
group was 0.8. In the extended dataset, the
incidence rate was 0.49 for the 2-milligram and
0.75 for the 4-milligram treated patients with
overlapping confidence intervals.

These rates are also consistent with those
reported from other RA clinical programs.
Potential major adverse cardiovascular events or
MACE were externally adjudicated in the phase 3
program. 4 events were reported in the placebo-
controlled time period, 2 in placebo and 2 in the
4-milligram group.

The overall MACE incidence rate was 0.5 for
the all bari RA dataset based on 38 events. In the
extended dataset, the rate was 0.16 for 2 milligram
and 0.54 for the 4 milligram. For context, the
rates reported with other RA clinical programs
ranged from 0.3 to 1.7.

Baricitinib was associated with changes in a number of laboratory values. First, we'll look at the categorical changes for specific hematologic and clinical chemistry values based on the percent of patients with a common terminology criteria for adverse events or CTCAE, grade 3 or worse change from baseline.

After that, we'll review the mean change from baseline up to 52 weeks for select analytes. Grade 3 changes or worse in hematology were uncommon to rare and uncommonly resulted in discontinuation. 1 to 2 percent of baricitinib-treated patients had platelets greater than 600,000 per mL with other hematologic changes noted less frequently.

For ALT, increases due to greater than 3 times the upper limit of normal were found at 1 to 2 percent for baricitinib-treated patients. Both Lilly and the FDA reviewed all increases greater than 10 times the upper limit of normal and concluded no baricitinib-induced liver injury.
Dose-related changes in creatine phosphokinase were also noted and did not result in adverse clinical outcomes. Increases in LDL to high or very high were frequent primarily due to an increase in large and a decrease in small LDL particles. And all laboratory changes shown here are included in draft labeling.

Let's move now to discuss mean changes over time. This line chart shows the time course of platelet count for the placebo, 2-, and 4-milligram dose groups up to 52 weeks. Baricitinib was associated with a dose-dependent increase in mean platelets within the first two weeks, which then returned towards baseline.

Importantly, the change in platelet count was not clinically correlated with thrombotic events. In recognition of the FDA's concern about the mechanism of platelet count increases, we explored further. Increased platelet production is one potential hypothesis for the increase in platelet count. It was the first mechanism we considered and was described by the FDA.
The increase in platelets would be from increased thrombopoietin at the bone marrow in the yellow circles, resulting in the production of younger, larger platelets. This would also increase mean platelet volume. Another hypothesis for increased platelet count is reduced platelet clearance. Reduced clearance would result in older, smaller platelets remaining in the circulation longer and this would decrease mean platelet volume.

We conducted an exploratory evaluation of mean platelet volume in a sample of baricitinib-treated patients and found a decrease in mean platelet volume, which is in line with the hypothesis of reduced platelet clearance. Other laboratory changes included decreases in absolute neutrophil count in the first 4 to 8 weeks, which then stabilized, largely remaining within the normal range.

Lymphocyte counts increased within the first week of treatment, then returned to baseline and stabilized at 12 to 24 weeks. Evaluation of serum
lipids show dose-dependent increases for cholesterol and triglycerides by week 12 that then stabilized.

Change in LDL cholesterol is shown here, with increases of 8 percent and 14 percent for the 2-milligram and 4-milligram doses. Statin initiation reduced LDL and total cholesterol. And LDL increases have been noted for other JAK and IL-6 inhibitors.

HDL increased in a similar dose-related manner and stabilized around 12 weeks. And the ratio of LDL to HDL shown here did not markedly change over time. And no association was found between lipid changes and MACE.

Let's now look at the potential thrombotic risk, including arterial and venous thrombotic events. It is known that RA patients have a twofold higher risk of venous thromboembolism and are prone to increased arterial complications, often due to accelerated atherosclerosis.

Shown here are the arterial thrombotic events from week 0 to 24 for the placebo-controlled
dataset and the 4-milligram placebo-controlled dataset. This second placebo-controlled dataset expands the placebo period. These data show no difference in frequency or incidence rate by dose. And over longer durations of exposure, we again note no difference.

Let's now look at the signal for venous thromboembolism or VTE, where we evaluated events of deep vein thrombosis or DVT and pulmonary embolism, PE. Extensive evaluation of the baricitinib clinical data has not confirmed a causal effect and has also not fully ruled it out.

It's therefore appropriate to consider VTE an important yet potential risk. During the 24-week placebo-controlled period, 6 events were reported in the 4-milligram group compared to none with placebo.

Shown here is a summary of individual data for the 6 patients with a VTE during that 24-week placebo-controlled period. 3 of these events were serious due to hospitalization and 3 were not considered serious. None of these cases were from
the U.S. and, in general, these patients were older, had a high body mass index or BMI, where 5 of 6 patients were severely or morbidly obese, and they had multiple other risk factors for VTE.

Five patients continued treatment, 3 after temporary interruption, 2 with no interruption. And for 1 patient, the VTE was not reported while on treatment, rather one month after discontinuation of baricitinib. Based on these differences, we look more closely at risk factors that could be associated with events.

Although baseline characteristics were balanced across treatment groups, we compared the frequency of a number of specific risk factors in patients with and without VTE. We conducted exploratory single and multivariable analyses using the all bari dataset. And from the single variable analysis, we found a number of variables associated with VTE which are highlighted here.

Of note, platelet counts at baseline, 2 weeks, or maximum change post-baseline were not associated with VTE. Also, we looked at all of
these in a multivariable analysis and found that previous history of VTE, age, BMI, and COX-2 inhibitor use at baseline were significant explanatory factors.

After including these, no other variables were associated with a higher or lower risk of VTE. We also looked at a number of VTEs in patients initially receiving placebo who were subsequently switched to baricitinib. In this group of 928 patients, 1 DVT was reported in the first 24 weeks of baricitinib treatment for an incidence rate of 0.2. This event was 2 days after a femur fracture where the patient was treated with aspirin, recovered, and continued on baricitinib.

Also, for the 451 patients switching to baricitinib from methotrexate or adalimumab, no VTEs were reported in their first 24 weeks of exposure. These rates, after crossover to baricitinib, were not suggestive of an acute drug-related effect. And consistent with the findings after crossover, VTEs were not clustered early in exposure as might be expected if baricitinib use
was causal. Rather, events accrued at a fairly steady rate of 0.5 percent per year with a range from the first baricitinib dose to VTE diagnosis of 37 to 1,658 days.

The linear rate of VTE occurrence suggests that the VTE incidence rate can be estimated using data from all baricitinib-treated patients. So the overall point estimate for VTE from the larger all bari RA dataset, up to 192 weeks, was 0.53 with a narrow confidence interval and an upper confidence limit of 0.7, providing the most robust and stable incidence rate estimate.

A dose relationship can be another indicator of possible causality. Although no events were reported by 2-milligram treated patients in the placebo-controlled period, the VTE incidence rates were 0.49 with 2 milligram and 0.48 with 4 milligram in the extended dataset.

So how do these results compare to what is expected in the RA population? We looked for additional data to put the baricitinib results into context. Although a number of published studies
from clinical trials of other RA therapies provide event numbers, most do not provide incidence rates or total patient-years of exposure.

We found this detailed information from one registration program, sarilumab, approved in 2017, with data on serious adverse events only. The incidence rates for serious PE and DVT from the sarilumab and baricitinib programs are shown here.

Because clinical trial data are limited, we evaluated the VTE incidence rate in RA patients using FDA's Sentinel Surveillance database, with health claims from over 70 million U.S. patients and Truven MarketScan data, also based on U.S. claims from 115 million people.

Here are the VTE incidence rates from patients initiating tofacitinib, conventional DMARDs, or biologics in Sentinel and Truven, including all patients regardless of age.

Also, the range in incidence rates noted in published observational studies is 0.33 to 0.79. While we acknowledge that observational data are not directly comparable to clinical trials, these
rates do provide some context for the background VTE incidence rate for RA patients.

In summary, we investigated the VTE imbalance in the placebo-controlled period and the evidence did not confirm causality. All events were in patients with 1 or multiple risk factors. An exploratory analysis showed history of VTE, older age, higher BMI, and COX-2 use were important explanatory variables.

An increased risk of VTE was not found for patients switching from placebo or active comparator to baricitinib. No temporal relationship was noted and there was no association with platelet counts. There was no dose response with long-term exposure and the overall incidence rate, 0.53. Although we could not confirm that baricitinib causes VTE, we also could not rule it out and have therefore made vet an important potential risk.

Globally, in the countries where baricitinib is approved, we warn prescribers to use caution in patients with risk factors for VTE, monitor, and
interrupt if an event occurs, then treat the patient and consider restarting baricitinib when appropriate.

We have also proposed a warning for the U.S. label. Warnings for other important potential and identified risks are also proposed and are one component of risk management. The post-approval risk management activities will further characterize the long-term safety profile.

Real-world observational studies will focus on serious infection, malignancy, MACE, and VTEs. We will look for safety signals from spontaneous adverse event reports, data from ongoing RA trials, and trials for other indications in our global development program.

For VTE, clinical trial events will be externally adjudicated and additional data and laboratory samples will be collected for further assessment of each event. The post-approval studies will evaluate data from approximately 13,000 patients treated with baricitinib.

A prospective observational study among
4,000 baricitinib-treated patients at both the 2- and 4-milligram dose compare the incidence of important potential risks with those among patients treated with biologics.

The total observation period will be 8 to 12 years for risks with longer latency and, at target enrollment, we will have 80 percent power to detect a twofold relative risk for VTE. We will also conduct a retrospective study based on RA patients enrolled in U.S. health plans.

Other studies include RA registries in Sweden, Denmark, Germany, and the U.K. for characterization of safety with long-term use and a prospective cohort of 3,000 baricitinib RA patients in Japan.

Since approval outside of the U.S., approximately 12,900 patients have received baricitinib with 3,500 patient years of exposure. From spontaneous adverse event reports, infections were the most common serious and non-serious event.

There were a total of 2 DVTs and 1 PE reported and no new safety signals were identified.
Early interim results from baricitinib post-approval registries demonstrate no new safety signals. No death, MACE, or VTEs have been reported from these recently initiated post-approval studies.

In summary, the data demonstrate that the 2- and 4-milligram doses of baricitinib have acceptable and manageable safety profiles. Based on additional exposures, we have more precise estimates of potential safety risks and, if shown, they are within the range of approved RA medicines.

Adverse events of special interest and baricitinib-related changes in laboratory values are included in draft labeling. The incidence rates of serious infection, malignancy, and MACE showed moderate differences by dose and these were within the range of rates reported for other RA therapies.

Venous thromboembolism is an important potential risk with an overall incidence rate of 0.53 and is addressed as a warning in our proposed U.S. label. Already underway is an extensive post-
approval risk management plan that will further characterize uncommon to rare safety risks that are better understood after long-term exposure.

Thank you for your attention. Dr. Josef Smolen will now provide his clinical perspective on baricitinib.

Applicant Presentation – Josef Smolen

DR. SMOLEN: Thank you and good morning. I am Josef Smolen. It is a pleasure to be here to provide my clinical perspectives on the data presented for baricitinib.

I'm an immunologist, internist, and rheumatologist by training. Indeed, I am partly trained in this very area, the arthritis and rheumatism branch at NIH in Bethesda, a great and memorable time for me and my family.

More recently, I became a translational scientist in outcomes research. I'm also a clinical trialist and was involved in the earliest clinical trials of biological DMARDs in rheumatoid arthritis and psoriatic arthritis. And I was also a co-principal investigator in the RA-BEACON study.
Moreover, baricitinib is already used in my clinic. So where does baricitinib fit into the current treatment landscape from my perspective? Before answering this question, let me please reiterate what Dr. Genovese has already alluded to, namely that despite many treatment options such as 5 different TNF inhibitors, 2 different IL-6 receptor antibodies, of which one was just recently approved, two biologics with other modes of action, and 1 JAK inhibitor, which is the only oral targeted therapy available in the United States today.

We still have an unmet need in rheumatoid arthritis. Our treatment target today is at least low disease activity or remission and the ACR70 response is a surrogate for this good outcome and widely reported in clinical trials.

So here, I have included the ACR70 rates from registration studies of various compounds in methotrexate insufficiently-responding patients. While these bars do not come from head-to-head trials, I've used them in several of my peer-
reviewed articles.

Where head-to-head trials were performed, they confirmed the similar efficacy of these different compounds. So here does baricitinib fit here? When we look at the JADV or RA-BEAM trial in which adalimumab and baricitinib were compared head to head, we can see that, in adalimumab-treated patients in green, the ACR70 rate is exactly what we would expect it to be in the context of the other agents, including golimumab, another anti-TNF.

In contrast, the ACR70 response in patients treated with baricitinib at 4 milligrams, shown in blue, reached 30 percent and this was significantly different from adalimumab. Thus, JADV is the first study where an RA treatment, namely baricitinib, demonstrated significant superiority to the standard of care biologic agent, adalimumab, both used with background methotrexate.

If we now look at patients who are TNF-inhibitor insufficient responders, we see lower ACR70 response rates than in methotrexate
insufficiently responding patients, namely in the range of 10 to 16 percent.

How does baricitinib compare here? Well, the 2-milligram dose provides efficacy within the range of all these other agents and the 4-milligram dose is at the top of the range. Of note, no other studies shown here included patients who had failed so many prior biologic therapies, both in number and in type and who were therefore in the highest need for another efficacious treatment.

Here, this efficacy was provided by baricitinib. Generally, we need additional treatment options so more patients with rheumatoid arthritis may achieve clinically relevant responses in the target.

The data I have shown reveal that baricitinib provides additional clinical benefits to patients across different stages of the disease with the highest response rates currently seen.

Let us now look at baricitinib using the SDAI, a well-accepted continuous measure of disease activity from two trials of baricitinib. In both,
the JADW and JADX studies, baricitinib at 2 milligrams and 4 milligrams was superior to placebo as early as week 1.

In JADW, in the most refractory patients studied, namely those who failed previous biologics, baricitinib, 4 milligrams, provided better clinical results. And these benefits were confirmed in a post hoc analysis of patients who failed at least 2 conventional synthetic DMARDs in JADX, which you can see on the right.

These data provide support for the use of both doses of baricitinib, with the 4-milligram dose being superior in the growing number of more refractory patients. Let me now move from this composite measure to a more detailed look at individual variables of disease activity.

Here on the left, we see that the 2-milligram dose shows a significant improvement in pain compared to placebo. The 4-milligram dose shows an even greater change of pain scores, one of the most important factors for patients.

The dotted line reveals that, by four weeks,
the 4-milligram dose produced a degree of
improvement that was already as large as 2
milligrams ever achieved during the full six months
of study.

One of the top questions rheumatologists get
from patients is how long will it take me to feel
better. Clearly, these data show that 4 milligrams
gets them there more quickly. On the right, we now
can see the reduction of swollen joint counts by
both the 2-milligram and the 4-milligram dose, with
a stronger response to the 4-milligram dose.

Reduction of swollen joints is important
because swollen joints are related to the
progression of joint damage, which leads to
irreversible disability.

If we now briefly look at progression of
joint damage, we see on the left that, indeed, both
doses of baricitinib inhibited progression of
damage in the more refractory population of JADX,
but the 4-milligram dose was more effective, in
line with the joint counts data that I showed you
on the previous slide.
On the right, we see that baricitinib at 4 milligrams inhibits progression of joint damage to a very similar extent as adalimumab, the biologic standard of care.

When discussing treatment options, a very common question that I am asked for by my patients is can I reduce my treatment. We can answer this question, too. When starting baricitinib at 4 milligrams, once patients achieve sustained low disease activity or remission, one can consider tapering to the 2-milligram dose.

In the baricitinib dose-tapering study, a large majority of patients maintained the good response in 2 milligrams and, of those who did not, most recaptured disease control upon returning to 4 milligrams. Thus, baricitinib is one of very few RA therapies that demonstrated clinical effectiveness upon tapering in a randomized blinded way, thus bringing to life the ACR and EULAR recommendations for dose tapering.

Turning to risks, the safety profile of baricitinib is similar to what we have come to
expect with biologics and JAK inhibitors. Serious infections are not more frequent compared to data from recent clinical trials. Rare events such as malignancies and MACE are also within the range of those observed with RA therapies.

As with other JAK inhibitors, herpes zoster was reported with baricitinib, but these events have been mostly mild to moderate and uncomplicated. Overall, both doses of baricitinib are within the range of other approved DMARDs.

Let me now turn our attention to venous thrombotic events. The risk of venous thromboembolic events should be monitored in clinical practice through ongoing studies and post-approval surveillance such as registries, which are already underway in countries where baricitinib is approved.

Overall, these rare events with typical presentations, which essentially did not occur when patients were switched to baricitinib from placebo or other drugs. Importantly, as internists and rheumatologists, we are familiar with risk
assessment, diagnosis, and management of thrombotic events.

Given the benefit that baricitinib can provide for RA patients, I feel that these events should not preclude the approval and use of this novel DMARD in the United States.

In summary, baricitinib responds to treatment armamentarium for moderate to severe RA. Baricitinib achieved consistent and significant benefits across the four domains of disease-modifying anti-rheumatic drugs, namely clinical signs and symptoms, physical function, progression of structural damage, and other patient-reported outcomes, even in the most refractory patients.

These benefits are achieved rapidly and, in my view, outweigh the known and potential risks which are familiar to and manageable by rheumatologists. And these benefits exceed those of standard of care therapies such as methotrexate and also adalimumab in patients who were unable to achieve treatment goals with current available therapies.
Both doses are supported by evidence and this allows for the use of different doses depending on where a patient is on the RA continuum. And I believe physicians can determine the right dose that brings the right benefit-risk balance to meet individual patients' needs here in the United States.

Thank you very much for your time and I'm pleased to invite Dr. Jim McGill to conclude the presentation and moderate the question and answer.

Applicant Presentation – James McGill

DR. McGILL: Thank you, Dr. Smolen. My name is Jim McGill and I'm a gastroenterologist and hepatologist. And I have been developing medicines for more than 20 years. Over the last six years, I've been developing medications for rheumatological illnesses.

I am privileged to be the development leader for baricitinib, responsible for its worldwide research program. I want to express my thanks to the FDA for organizing this advisory committee and for your participation today as we discuss what I
believe is a common goal, helping more patients
with RA achieve better clinical outcomes and an
improved quality of life.

Since our original submission to FDA, baricitinib has been approved in more than 40
countries, including the E.U. and Japan, and no new
safety signals have been detected. Our
resubmission provided a nearly 90 percent increase
in patient years of safety exposure, which has
increased the number of patients ever treated with
2 milligrams, allowing better characterization of
the 2-milligram dose.

With this overall greater exposure, we have
also been able to more precisely determine the
incidence rate of VTE and we are currently and will
continue to further evaluate this and other rare
events in post-approval studies.

Lilly's recommendation for how physicians
can effectively use both the 2-milligram and 4-
milligram dose is driven by the need we still see
with patients who struggle every day to manage
their RA despite the availability of other
therapies.

   Our intent is to provide both doses as options so that the physicians can make an affirmative benefit-risk decision, balancing an individual patient's need for disease control against potential safety risks.

   In closing, we want to thank the many investigators and their teams for the 10 years of work summarized this morning and particularly thank the thousands of patient volunteers who participated in our trials. Lastly, we do want to thank you, the members of this advisory committee for your attention and diligence in this review process. We welcome your questions.

Clarifying Questions

DR. SCHER: Thanks very much to the applicant. We are going to open the panel for clarifying questions. Just remember to state your name. We're being recorded. And if you can, please direct the questions to a specific member. Dr. Bilker?

DR. BILKER: I have a question that's
specifically about those patients who are on two or more DMARDs.

So they appear to have the greatest benefit of baricitinib, specifically the 4-milligram dose. Considering the risk profile of baricitinib, they appear also to have the highest risk. In the documentation provided, there's a statement.

It refers to table 34 in the Lilly briefing and it's stated that the overall safety profile of baricitinib in the 2 or more DMARD inadequate-responder subpopulation was consistent with findings from the overall baricitinib-treated population.

But if you look at the table, table 34, there do appear to be some potential differences. And what I wanted to know was where their statistical performed to assess the subgroup on the safety profile measures differences to the other groups and I'm concerned that they may have both the greatest benefit and the greatest risk.

DR. McGILL: So is this table 34 from the briefing book correct?
DR. BILKER: From the Lilly document, the Lilly briefing document. He referred to it in the talks.

DR. McGIN: Yes. Dr. Veenhuizen, can you comment on that, please?

DR. VEENHUIZEN: Melissa Veenhuizen, Lilly global patient safety. We did not do formal statistical analyses to compare these incidence rates because our safety data is primarily descriptive. And as you can see, these are fairly low Ns in this separation of the program and the patient years, but we did try to provide it by incidence rates to show a relative comparison to the populations presented elsewhere.

DR. SCHER: Dr. Oliver?

DR. OLIVER: Alyce Oliver. Do you propose that the indication for baricitinib will be in combination with methotrexate?

DR. McGIN: Yes. For most patients, it would be in addition to methotrexate as our studies have included. However, there are patients who are intolerant and we've studied those as well. And
most of those patients can get a benefit as well depending upon the patient's tolerance.

DR. OLIVER: Do you have data with baricitinib monotherapy with adalimumab as the comparative?

DR. McGILL: Without methotrexate?

DR. OLIVER: Yes.

DR. McGILL: I think the best study is the one that we did on the naïve, but Dr. Rooney, can you say more on that, please?

DR. ROONEY: Thank you. Terence Rooney, Lilly. The monotherapy data primarily come from the JADZ trial in DMARD-naïve patients, where you had methotrexate monotherapy, baricitinib monotherapy, or the combination.

We didn't conduct our comparison to adalimumab without methotrexate. In fact, we specifically required background methotrexate to give the ada arm the best chance to succeed. So that's the short answer to your specific question about monotherapy head to head versus adalimumab.

We instead elected to go head to head in the
setting where adalimumab performs best.

DR. SCHER: Dr. Brittain?

DR. BRITTAIN: Hi. I have two quick questions. With respect to safety, I understand why you did the integrated analyses the way you did, to maximize the number of patients, but there's a potential for sort of an apples and oranges comparison because not all the studies have the low dose. Did you do any comparisons, integrated analyses just using the trials that had 2 to 4 head to head?

DR. VEENHUIZEN: Yes. In our original submission and in the resubmission, we provided that information to the FDA comparing those. And if you have something specific that you would like to look at, we can do it, you know, for specifics.

DR. BRITTAIN: So the conclusions were similar when you looked at just the trials with the head-to-head comparison?

DR. VEENHUIZEN: They were, yes.

DR. BRITTAIN: With respect to efficacy, let's look at CO-40. So certainly, this is an
interesting slide. Did you do any tests of interaction to see if there was really a difference in the treatment effect between 2 and 4 in these two subgroups?

DR. McGILL: Dr. Beattie?

DR. SCHER: Sorry. A reminder to state your name before you start speaking or asking questions.

DR. BEATTIE: Scott Beattie, Lilly Statistics. Yes, indeed we did do interaction testing. We did that in response to the response letter in this particular post hoc analysis. And what I can do is show you this particular slide, which shows from this study and these two subgroups, at weeks 12 and 24, the results of the two continuous endpoints that we focused on for comparison between effective treatments and doses.

For SDAI and DAS28, you'll see that interaction tests were positive in 2 of the 4 cases and very close to our threshold of .1 for the other two, indicating that 2 and 4 were quite similar in the subgroup of patients who had only one prior DMARD for experience and those for 2 or more, that
there was a benefit favoring 4.

DR. SCHER: Ms. Aronson, please?

DR. ARONSON: Excuse me. Diane Aronson.

I'd like to see if I could see two slides in relationship to the design. And it might be Dr. Genovese. But is there a slide that shows the list of exclusions?

DR. McGILL: Do we have a list for the exclusions? Dr. Rooney?

DR. ROONEY: Thank you. Terence Rooney, Lilly. I don't think we have a simple slide for the exclusion criteria because of course, there were many. Is there anything I can clarify for you?

DR. ARONSON: Wow. I'd just like to know who was excluded from the study, yes.

DR. ROONEY: So the inclusion criteria aimed to enroll patients who had moderately to severely active RA in the particular line of treatment that was being studied. So there would have been inclusion and exclusion criteria around previous and background therapy to make sure that we
captured the relevant population.

So a good example, for example, would be in study JADW, where the patients had failed previous biologics, they were required to have failed at least 1 TNF inhibitor, but kind of in contrast to a number of recent development programs, there was then no upper limit on the number or nature of prior biologics.

Hence, I tried to highlight we ended up with a very refractory population. On the safety side, then, we had a variety of fairly well established exclusion criteria in people who were vulnerable, or unstable, or sick at the time of entry that included medical factors and laboratory testing during screening.

But again, if there's a specific measure I can help clarify, I'd be happy to.

DR. ARONSON: So for the post-market post-approval studies, was it the same exclusions?

DR. McGILL: Dr. Veenhuizen?

DR. VEENHUIZEN: Melissa Veenhuizen, Lilly Patient Safety. For the post-approval studies,
those will be observational primarily that we have begun in registries. And that would be any and all patients as prescribers choose to put patients on baricitinib. We will collect data from them, no exclusions.

DR. ARONSON: So the thrombotic risk was not sort of pulled out.

DR. VEENHUIZEN: For the thrombotic risk specifically, from clinical trials, we will collect information. And if we do receive spontaneous adverse event reports or those in the registries of the post-approval studies, we will attempt to collect more additional information, but we don't have that highlighted as specifically trying to include or exclude based on any risk factors.

DR. ARONSON: Then the second slide I wanted to ask about is concomitant medications. Do you have the list of either required? I know that methotrexate, the two DMARDs, but then also the optional ones that could be taken.

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thanks, if could bring up maybe
the cartoon of the program. Terence Rooney, Lilly.

Some of the individual studies required particular background therapies for a variety of reasons.

For instance, here we are. I'll bring up the slide. So you can see the cartoon overview again, just to refresh your memory, of the design of the phase 3 program. In the naive trial at the top, patients weren't receiving any background DMARD therapies because they were naïve patients.

The second study contained a specific measure to make sure that the adalimumab arm had the best chance of success. So that particular measure was that the patients were required to be receiving background methotrexate.

The other third study, RA-BUILD, patients were not required to be taking background conventional DMARDs that they had failed. They had to have failed some previous background conventional DMARD in the past, but a small proportion actually came in on no background therapy.

These would have been patients whose last
DMARD they had failed, they weren't tolerating. So they came in and, interestingly, the response to baricitinib in that monotherapy setting, albeit in a small subgroup of patients, was quite consistent with the overall.

Finally, then, the last study, RA-BEACON at the bottom; these were people who had failed multiple previous therapies, including biologics. So we wanted to make absolutely sure that these folks from an ethical perspective were receiving some background treatment, so they were required to be taking background cDMARDs.

DR. ARONSON: So as patients, we sometimes feel like we play a Russian roulette with our potential side effects. Do you have any safety or efficacy data on just taking the drug alone?

DR. McGILL: Dr. Veenhuizen or Dr. Rooney, do you have that from the Z? May I ask also if a question is about drug-drug interactions? I'm trying to understand if that's an element of your question. There's a concern about, are they taking other medications that would interfere. Is that
also a part of it or not?

DR. ARONSON: Trying to parse out, too, the
drug with other concomitant meds.

DR. ROONEY: Thank you. Terence Rooney,
Lilly. Maybe I'll begin with the efficacy side and
hand over to one of my safety colleagues for the
safety side. So we conducted them. JADZ, please,
if we could get that up. Your question is about
monotherapy. Our trial that was the principal when
evaluating monotherapy was in DMARD-naïve patients.
That was study JADZ.

So that study demonstrated that baricitinib,
4 milligrams, whether used alone or in combination
with methotrexate showed superior efficacy to
methotrexate monotherapy and it was a double blind,
double dummy approach.

I'll show you a very representative sample
of those outcome measures. I think one nice way to
bring it to life is to look at the individual
components of the composite scores because that
gives you a nice cross-section of the consistency
of response.
These panels show the change from baseline through the full year of the trial for the joint counts on the left, for the global assessments on the right. So that's the physician at the top and the patient at the bottom. And we consistently saw that each baricitinib-containing AR was superior to the active comparator, methotrexate.

But the purple-colored monotherapy line showing significant improvement from the earliest week sustained throughout a year. Interestingly enough, we also saw that combination therapy and monotherapy were quite comparable.

The second and final slide I'll show you is the remaining components of the core set, pain on the left top, physical function at the bottom, and then finally rounding it out, the acute phase markers at the right-hand side.

So within that prospective randomized study, baricitinib monotherapy was clearly efficacious and in fact more efficacious than the active comparator, methotrexate.

DR. SCHER: Thank you. Dr. Katz, please?
DR. KATZ: James Katz. You showed some data, if I understand correctly, that venous thromboembolism has no dose response curve. I have a couple of questions about that. The first is, is this data control for concurrent aspirin and Plaquenil?

DR. McGill: Is it absent a control?

DR. KATZ: It is controlled for concurrent aspirin and Plaquenil or Plaquenil?

DR. McGill: We have information about the use of those drugs, but it wasn't controlled for those medications. Robert, do you have that, Dr. Baker?

DR. Baker: Hello, Robert Baker. I'm a leader for global patient safety at Lilly. The trial that you saw was straight exposure-adjusted comparison, but what we also referenced today is we had done looking across the program at a multivariate analysis that included both doses, a number of concomitant medicines, including those that would have platelet effects.

None of those came out as independent
variables. So we don't have a direct answer, but that study would suggest there wasn't an interaction.

DR. KATZ: While you are at it, the dose response curve -- did you do the analysis based on the drug serum concentration?

DR. McGILL: Actually, Dr. Xin Zhang has done some work on that to answer that question, I believe.

DR. ZHANG: Xin Zhang, PK/PD, Eli Lilly. Yes, we did evaluate that. As you can see in this slide, we compared Cmax at peak concentration and AUC. You can think of it as a total daily drug exposure. And in each plot, the boxes on the left-hand side are for patients without an event. On the right is with an event DVT. As you can see, they're quite comparable.

DR. KATZ: But I notice the error bars. Can you help me interpret that a little bit better?

DR. ZHANG: Definitely. So the box plot here shows the distribution of the concentration. So the boxes is for the 25th and the 75th
percentiles and the risk curves are for the 5th and the 95th percentiles.

Of course, we have less patients, a small number of patients with an event. So you can see that difference in the bar.

DR. KATZ: I have one other separate question.

DR. McGILL: Yes.

DR. KATZ: The dose reduction study from 4 to 2 milligrams; did you follow the Sharp Score progression after dose reduction?

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thanks, Terence Rooney, Lilly. We did, but I don't have a change from stepdown baseline analysis in Sharp score to show you. The simple reason for that is, to do that, we would have had to have taken an x-ray at the time of randomization to stepdown.

That would have broken one of the blinding elements of the study. We really wanted to make it robust. There were two blinding elements to that stepdown experiment. One of course is that, when
the patients were randomized to stay on or step down, they didn't know the dose.

But the other one was that it happened silently. They actually didn't even know that it was happening. So they would enter the disease activity scores at the visits and, if the patients met the criteria, sustained low disease activity or remission, the system would just quietly randomize them in the background.

DR. SCHER: Thank you. Dr. Kim, please?

DR. KIM: Thank you, Seoyoung Kim. So I have a question. In slide CO-28 and, sorry, CO-40, where the slide says over 2 or 2 DMARDs failed, does it include just synthetic conventional DMARDs or in this slide in particular includes biologic or even tofacitinib?

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thank you, Terence Rooney, Lilly. This is from the study JADX, where patients had never received an injectable biologic therapy. These patients had all failed at least one previous oral conventional DMARD. So the prior therapy, one
only or multiple, refers to conventional DMARDs.

DR. KIM: What was the second most common conventional DMARD after methotrexate?

DR. ROONEY: Can we get the baseline characteristics from study JADX? So you'll see we permitted a wide range of -- actually, let me clarify first. Are you asking about concomitant or prior?

DR. KIM: I guess either because of how you counted two or more. Right?

DR. ROONEY: Concomitant is probably the easiest. Well, the two or more, just to clarify, refers to ever. So two or more refers to concomitant and ever in the past.

If you look at the baseline on concomitant medications in study JADX, as you highlighted, as you would expect, methotrexate was the commonest, about three-quarters of the patients. And then you can see the rank ordering going down, Plaquenil in second place, leflunomide in third, and sulfasalazine in fourth, so pretty representative.

DR. KIM: My second question is, in one of
the talks, it was mentioned the increased number of platelet count was not associated with the risk of thrombotic events. I was wondering if we could get a little more detail, like what kind of analysis or statistical analysis has been done.

DR. McGILL: Dr. Baker?

DR. BAKER: Thank you, Dr. Kim. Robert Baker from Eli Lilly. We looked at that in a number of ways. Firstly, we looked at individuals who had events and looked for abnormalities or pattern of events. And we did not find those. Out of the total program, the 42 events we saw, only 6 had elevated platelet levels at the point where it occurred.

Now, overall, about half of patients get elevation at some points, so a second suggestion that these are not related phenomenon is what you see regarding platelets, which are an effect of baricitinib, where you see the sharp increase that you saw relatively early in treatment.

That does not correspond to the pattern of venous thromboembolic events which occur very
gradually and consistently over the course of the
treatment. Secondly, the drug effect of platelet
increase is a dose-related phenomenon. We did not
find that for the VTEs. So that suggests that they
are not related to each other.

Then, when you do a simple comparison such
as the ones that we had shown a little bit ago of
people with events and without events, the hazard
ratio is when we look at either increasing
platelets over a level of normal, a large increase
in platelets. The hazard ratio is about flat for
those who had events and those who didn't have
events.

Then finally, as Dr. Veenhuizen alluded to,
were've been doing some work on the biology of
platelets, which also doesn't substantiate this.

DR. KIM: Then lastly, I have a question
related to CO-84 and 85. Can you explain how this
multivariable univariable analysis was done? If I
understand the slides or presentation correctly,
there was no event in the placebo group at all.
Right? Or the thrombotic?
DR. McGILL: In the placebo-controlled period, there were no events. That's correct.

DR. KIM: So these risk factors were assessed among the baricitinib-treated patients only?

DR. McGILL: Dr. Beattie will try to answer your questions.

DR. BEATTIE: Yes. For this particular analysis, we looked at all the patients who received baricitinib by any means, meaning from randomization or from switch from other treatments, so it was using the totality of the data to assess these risk markers.

DR. KIM: So the incident rate for 0.53 per 100 was for both 2-milligram and 4-milligram baricitinib groups. Right?

DR. BEATTIE: When we had done an analysis from the extended dataset, the incidence rates for the two dose groups were very similar to each other and around that .5 estimate.

DR. KIM: Then it was 0 for the placebo. So if I do a back-of-the-envelope kind of calculation,
the number I need to have for the thrombotic event is actually less than 200 patients. I don't know if you guys did the calculation that way.

DR. BEATTIE: If you are doing something on a per-100-patient-years basis, right, yes.

DR. KIM: Thank you.

DR. SCHER: Thank you, Dr. Kim. We will have time for three more questions. I will remind you that there will be an extensive discussion time set aside in the afternoon. So Dr. Russell, please?

DR. RUSSELL: Thank you, Dr. Russell. On slide CO-61, we have listing of deaths associated with various studies and various dosages. Could we have the cause of death on those who died in the baricitinib studies?

DR. McGILL: Yes. Dr. Veenhuizen?

DR. RUSSELL: Yes.

DR. VEEENHUIZEN: Melissa Veenhuizen, global patient safety. When you are looking at cause of death, are you looking for, for example, if we provide system organ class? Would that be helpful
for you?

DR. RUSSELL: Yes.

DR. VEENHUIZEN: So this is deaths as treated, so this would be deaths when they occurred whether they were on placebo, 2 milligram, 4 milligram, and then the total from the all bari dataset on the far right column. As you can see, the majority of these events were cardiovascular, followed by infections, malignancies, and then respiratory, and a smattering of others, similar to what Dr. Genovese had mentioned as the most common causes of death for RA patients.

DR. RUSSELL: One more question in regard to the causes of the thrombosis. Females are more likely to have thrombosis and RA patients are more likely to have thrombosis. I was surprised that female gender was not a risk factor for the thrombosis that was, I'm sure, examined and was not found.

DR. McGILL: Dr. Beattie?

DR. BEATTIE: Scott Beattie. Yes, we did look at that, I believe just because it's such a
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rare event and we're looking at about 8,000 patient
years, there's not enough data to really assess
gender in this specific dataset.

DR. SCHER: Thank you. Dr. Caplan, please?

DR. CAPLAN: Liron Caplan from Rocky
Mountain, regional VA. First question, was there a
balance between or was there an imbalance between
the placebo and the baricitinib in terms of BMI and
age? And I'm referring to CO-82.

DR. McGILL: Dr. Veenhuizen?

DR. VEENHUIZEN: So if you follow this with
the next slide, which talks about the patient
characteristics of those that had events, CO-83 in
the core deck. You can see that these patients
were generally older. By that, we mean they're at
least over 50. I don't want to insult anyone. And
the BMIs were rather high in this population. And
we did find that older age in the multivariable
model and higher BMI were explanatory variables for
the events that we observed.

DR. CAPLAN: My question is whether there
was an imbalance in BMI and age.
DR. VEENHUIZEN: At baseline?

DR. CAPLAN: Yes, between the two groups, between the intervention group and the control groups.

DR. VEENHUIZEN: At baseline, the majority of the baseline characteristics were fairly well balanced. There was a 16 percent versus 20 percent as far as older age. And so the imbalance was in favor, essentially, of the placebo group, so we did have an older population in the baricitinib-treated patients at baseline.

DR. CAPLAN: I'm sorry. What does that mean, 16 percent older age?

DR. VEENHUIZEN: When we looked at the percentage of the population.

DR. CAPLAN: Over age 50, is that how you define that?

DR. VEENHUIZEN: This is the demographics and the risk factors at baseline for the different datasets and I believe you can see here, when we looked at the age categories, you look at the greater than 65 row, which would be the third from
the top. 16 percent of the placebo group were over 65, whereas 20 percent of the baricitinib group were over 65 and that was the only variable that was significantly different based on baseline demographics.

DR. CAPLAN: Then there were a number of slides from around CO-64 to 69. Were formal comparisons done between the placebo and the intervention in terms of infection, malignancy, lab results?

DR. McGILL: Can I see some of those slides, just so I follow the question more completely? CO-64, you're looking for statistical comparisons? Is that the question?

DR. CAPLAN: Yes, that's the question.

DR. McGILL: Dr. Beattie, could you answer? Or Dr. Veenhuizen?

DR. VEENHUIZEN: Regarding formal statistical comparisons of the safety data, they were not done. Again, the safety data is descriptive and, in this integrated dataset, all we were trying to do is explain the differences that
we had seen between the populations. And so those moderate differences were not tested for statistical significance.

DR. SCHER: Thank you very much. The last question of the discussion, Dr. Ortel, please?

DR. ORTEL: Thank you, Tom Ortel. Just to follow up on the earlier question, I wanted to make sure that, in the clinical trials that were performed, did the exclusionary criteria include high-risk thromboembolism patients, such as patients with prior VTE, patients on chronic anticoagulant therapy, patients constantly taking HRT, things like that?

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thanks, Terence Rooney, Lilly. No, we didn't have any specific criteria around BMI or VTE risk. We had general guidance that's very consistent across RA development protocols that any patient who had any chronic or acute disease that rendered them in the opinion of the investigator unsuited just in general terms and then we had some specific measures around other topics that are well
established in RA care, like recent malignancy and so forth.

But there were no exclusion criteria for patients with high risk of VTE. And so indeed, we did receive a population that was a good cross-section of prior VTE risk, including those very high BMI patients that were highlighted by patient characteristics in the placebo-controlled period.

DR. ORTEL: But just to clarify, prior VTE did not exclude somebody, did not?

DR. ROONEY: No.

DR. SCHER: Thank you. I'm going to ask the last question if you allow me. It was commented upon that the efficacy of bari 4 milligrams has been consistently superior in every single phase 2, phase 3 trial, and the outcomes has been, as usual, the primary endpoint ACR20. What's useful in general is to look at the deltas when we describe efficacy compared to other clinical trials.

I note that, in JADV and JADX, the placebo response is rather high at about 40 percent. Is there an explanation or anything that you can
comment on in terms of comparison to other trials?

   DR. McGILL: Dr. Rooney?

   DR. ROONEY: Thanks, Terence Rooney, Lilly.

   We took a look at that and let's focus on perhaps
   JADV, which was the largest of the studies, the
   head-to-head versus adalimumab. I'll bring up a
   slide here that I think makes the point that the
   placebo response rate there actually matches pretty
   well to placebo responses with respect to that
   primary outcome measure, ACR20, in recent
   contemporary studies.

   So here it is, represented a recent sample.
   You've got tofacitinib on the left, another JAK
   inhibitor in development, upadacitinib, the second,
   sarilumab, the last approval here in the United
   States from late last year, and then baricitinib
   from JADV.

   So when you look back over the last 20 years
   of RA clinical trials, we see our response rates
   have gone up. I think ours were in line with
   contemporary studies. That was our conclusion.

   DR. SCHER: There seems to be a differential
between, if you go back to that slide -- and I'm going to finish with this comment -- specifically with tofacitinib, there's a differential of about 10 points. Was that surprising?

DR. ROONEY: Again, the more recent studies, as you can see, upadacitinib is still in development and not yet submitted, but has reported out that placebo response rate is in the mid-30s, sarilumab also in the mid-30s. The most recent approval -- the sarilumab program really would have overlapped with the baricitinib program in terms of enrollment around the world, so that's perhaps the best comparison.

DR. SCHER: Thank you very much. So we will conclude this clarifying question session. So we will be taking a break of about 15 minutes. A reminder for the panel members not to discuss anything related to this session with any members of the panel or anybody inside or outside the building. We'll reconvene at 10:25.

(Whereupon, at 10:11 a.m., a recess was taken.)
DR. SCHER: Thanks for coming back. I would ask you to take a seat. We will be proceeding right now with the FDA presentation. Thank you.

FDA Presentation – Robert Abugov

DR. ABUGOV: Good morning, everyone, and thank you, Dr. Scher. I'm Robert Abugov, the statistical reviewer for this application. And I'll be discussing the efficacy of baricitinib.

To support the proposed usage of baricitinib, the applicant provided efficacy data which will be the subject of my presentation.

As has been mentioned earlier, the applicant has proposed a dose of 2 milligrams once daily. However, for patients with an inadequate response or intolerance to more than one DMARD, the applicant proposes a dose of 4 milligrams once daily.

In this presentation, we'll first discuss the efficacy of baricitinib compared to placebo. We'll see that baricitinib, 2 milligrams and 4 milligrams, are both highly effective for improvement of clinical response and physical
function in RA.

We'll also see, for inhibition of radiographic progression, that the 4-milligram dose is effective while there is still some uncertainty about the effectiveness of the 2-milligram dose.

Next, we'll compare efficacy of the 4- and 2-milligram doses. Individual phase 3 study results and an integrated analysis of four studies did show some differences between the 4-milligram and 2-milligram doses, but the differences were small.

We'll then reexamine the applicant's subgroup analyses which seem to imply that the benefits of the 4-milligram dose are enhanced compared to 2 milligrams among patients who lack response or who are intolerant to 2 or more DMARDs.

In particular, we'll show that there is no evidence to support the contention that the difference between the two doses is larger in this particular patient subpopulation. And finally, we'll wrap things up with a statement of our overall conclusions regarding efficacy.

Let's now begin by examining the efficacy of
baricitinib for clinical response and physical function.

As has been mentioned, there were four confirmatory studies in the phase 3 program. The 4-milligram dose was included in all of those studies while the 2-milligram dose was included in only two of those studies, JADX and JADW.

All four of these trials included ACR20 response, HAQ-DI, and DAS28 as primary or secondary endpoints. Additionally, in study JADV, the pre-planned analysis hierarchy included a measure of radiographic response, the modified Total Sharp Score as a major secondary endpoint.

The proportion of patients achieving ACR20 response was the primary endpoint in all four of the pivotal studies. It was analyzed using logistic regression, including any stratification variables used in the randomizations.

The final two columns of this table compared the two doses of baricitinib to control. You can see that, in all four studies, both doses significantly improved ACR response compared to
placebo.

The probabilities of response are roughly 50 to 70 percent on baricitinib as compared to 30 to 40 percent on placebo. For study JADZ, which enrolls only patients naive to methotrexate, both baricitinib monotherapy and baricitinib added to methotrexate provided response rates superior to methotrexate alone.

Change from baseline DAS28 and other continuous endpoints such as HAQ-DI and modified Total Sharp Score were analyzed using analysis of covariants, including stratification variables from the randomizations, as well as the baseline values.

Again, in the two right-hand columns, you can see highly significant effects of baricitinib compared to control. Mean differences between the baricitinib doses in control ranged from roughly minus .7 to minus 1.2.

Here are results from HAQ-DI, a continuous patient-reported outcome for functional ability, which is measured on a scale from 0 to 3. Again, in the two right-hand columns, you can see highly
significant effects of baricitinib compared to
control.

Estimated mean differences between the two
baricitinib doses in control were roughly minus .2
to minus .3 across these phase 3 studies.

For approval of an RA drug, we generally
require efficacy for clinical response. While
efficacy for radiographic response is not required
for approval, we consider it an important aspect of
treatment. It was analyzed as a major secondary
endpoint in study JADV, but was not included in the
analysis hierarchy for study JADX.

Regarding radiographic response in study
JADV, both baricitinib 4 milligrams and active
control, adalimumab, showed highly significant
effects compared to placebo, regardless of whether
only observed data was included or if instead
missing values were imputed via linear
extrapolation.

Of note, this study did not include the 2-
milligram dose. For study JADX, which was much
smaller than JADV, the 4-milligram dose again
provided statistically significant improvements compared to control, regulated of whether only observed data was included or instead missing data was imputed via linear extrapolation.

However, the results for the 2-milligram dose were weaker. The statistical significance compared to control was seen only in an analysis relying on linearly extrapolated data. For both doses, inclusion of linearly extrapolated data roughly doubled the point estimate of treatment effect.

The submission also included a single study, JADV, which provided a direct comparison of baricitinib, 4 milligrams, to adalimumab.

The results suggest greater efficacy of baricitinib, 4 milligrams, compared to adalimumab for ACR20 response and DAS28. However, the evidence is only from a single study and the estimated differences are moderate at 10 percentage points for ACR20 response and minus .28 for mean change in DAS28.

For radiographic progression, the difference
between baricitinib, 4 milligrams, and adalimumab was not statistically significant.

In conclusion, baricitinib, 2 or 4 milligrams, are both effective for improvement of clinical response as well as physical function in RA. For radiographic response, 4 milligrams is effective while there is still some uncertainty regarding the effectiveness of the 2-milligram dose.

Next, we compared the efficacy of the 2- and 4-milligram doses of baricitinib to help inform a benefit-risk comparison of these two dosing regimens. We start with the results of the two phase 3 studies, which included both of these doses.

Study JADW, as you'll recall, only enrolled patients who had failed to respond to at least 2 DMARDs, one conventional and one Tumor Necrosis Factor inhibitor.

The analyses presented here include ACR20, 50, and 70 responses as well as change from baseline, HAQ-DI. These endpoints are consistently
considered of sufficient importance for inclusion on RA product labels.

I also include change from baseline DAS28, a continuous measure which may be more sensitive to differences in clinical response than binary responder endpoints such as ACR20.

In study JADW, the 3 ACR responses in changes from baseline DAS28 and HAQ-DI seem to numerically favor the 4- over the 2-milligram dose. However, of these 5 endpoints, only 1 confidence interval, that for DAS28, excludes the null hypothesis of no difference between the doses.

Further, all of the differences are relatively small with a lot of uncertainty around the point estimates. For example, the estimated ACR20 response probabilities for 2 and 4 milligrams are 49 and 55 percent respectively for an estimated absolute difference of 6 percentage points, an odds ratio of 1.3, and with a very wide 95 percent confidence interval ranging from .8 to 2.0.

On the other hand, in study JADX, which enrolled patients regardless of number of prior
DMARDs, the 4-milligram dose provided no numerical advantage over 2 milligrams for ACR responses, with odds ratios for ACR responses at or below unity.

Similarly, results for the continuous variables, changes from baseline DAS28, and HAQ-DI do not consistently favor the 4- over the 2-milligram dose.

When considering approval of a treatment, we generally evaluate effects using results from each study separately. However, the individual studies were not powered to detect differences between the baricitinib doses.

FDA therefore additionally requested that the applicant provide support of integrated analyses, which used data from all of the available studies, which randomized patients to both of these doses.

The goal of this was to gain further precision regarding differences in efficacy between 4 and 2 milligrams. The integrated analyses included not only JADX and JADW, which we've already been discussing, but also included earlier
dose-ranging studies JADA and JADN, which enrolled RA patients with an inadequate response or intolerance to methotrexate.

For ACR20, the integrated analyses showed a small improvement in response for 4 over 2 milligrams at earlier time points. However, the improvements seemed to diminish over time and are small, with only a 2-percentage point estimated difference between the two doses by week 12.

Mean changes from baseline in DAS28 and HAQ-DI are also in a direction favoring 4 milligrams over 2 milligrams with 95 percent confidence intervals which exclude the null hypothesis of no difference between the two doses.

However, the estimated differences are quite small and those same confidence intervals also rule out improvements as large as commonly used estimates of minimal clinically important differences, equal to .6 for change from baseline DAS28 and .22 for change from baseline HAQ-DI.

So in conclusion, although the integrated analyses do suggest some differences in efficacy
between the 2- and 4-milligram doses, those

differences seem to trend downward over time and,
more important, they are likely quite small and
below commonly used estimates of minimum clinically
important differences.

It seems safe to say that the 4- and 2-
millgram doses of baricitinib are essentially on
or near the plateau of the dose response curve. As
previously discussed by Dr. Nikolov, the applicant,
in the response to our CR letter requested a change
in the dosing regimen to reflect a purported
increase in the efficacy of the 4-milligram over
the 2-milligram dose in the subpopulation of
patients who were inadequate responders or
intolerant to 2 or more DMARDs.

In particular, the applicant noted some
trends toward improvement on the 4 milligrams
relative to the 2-milligram dose in study JADW,
which was conducted in this inadequate responder
subpopulation and also emphasize some post hoc
analyses on this subpopulation in study JADX.

We next present those subgroup analyses and
discuss issues with the applicant's interpretation of the results. Some analyses for study JADX in the subgroup of patients who had active RA despite at least 2 prior DMARDs do seem to suggest a trend favoring the 4- over the 2-milligram dose for ACR responses.

However, the estimated differences are small and none of the confidence limits exclude the null hypothesis of no difference between the two doses.

In particular, ACR50 response in mean change from baseline DAS28 seemed to favor the 4-milligram dose. However, estimated ACR20 and ACR70 responses in mean changes for HAQ-DI are nearly identical for the two doses.

Like the general population, all of the estimated differences are small, with confidence intervals which rule out differences in DAS28 and HAQ-DI as large as the commonly used estimates of minimal clinically important differences.

In addition, I conducted an interaction test for the data from study JADX to see whether the treatment effects were different according to
number of prior DMARDs. For the primary endpoint, week 12, ACR20, the p value for the treatment effect by subgroup interaction test was .23, indicating no evidence that effects might be different among patients with an inadequate response to 2 or more prior DMARDs.

To illustrate that the subgroup differences emphasized by the applicant may be chance findings, I repeated these analyses again in study JADX, but in a complementary subpopulation; that is, among patients who had an inadequate response to fewer than 2 prior DMARDs.

Using the applicant's methodology actually suggests that the 2-milligram dose is superior to the 4-milligram dose in patients who had fewer than 2 prior DMARDs. Such a conclusion seems implausible.

It again argues against drawing any conclusions from this type of post hoc subgroup analysis in which differences between the doses are small, uncertainty is great, and there is no evidence of an interaction between subgroup and
treatment effect.

In summary, the subgroup analyses emphasized by the applicant do not change the conclusion that efficacy differences between the doses are likely very small. The statistical evidence does not support the applicant's claim that the benefits of the 4-milligram dose are enhanced compared to the 2-milligram dose among patients who have active RA despite prior experience with 2 or more DMARDs.

The results provided by the applicant were largely post hoc. The differences between the doses were small and not statistically significant. There was no convincing evidence of an interaction between subgroup and treatment effect. And use of the applicant's methodology in the complementary subpopulation suggest conclusions which seem implausible.

Thus, the subgroup analyses do not provide convincing evidence to support differing dosing regimens based on number of prior DMARDs.

Let's now sum things up here. Both the 4- and 2-milligram doses of baricitinib are effective
for clinical response and improvement in physical function in patients with RA. There are likely differences in efficacy between the 4- and the 2-milligram doses. However, if those differences exist, they are likely very small.

And finally, the subgroup analyses provided by the applicant don't change these conclusions and do not support a proposed dosing strategy which depends on number of prior DMARDs.

Thank you very much for your attention. Next, Dr. Raj Nair will present our safety findings.

**FDA Presentation - Raj Nair**

DR. NAIR: Good morning. My name is Raj Nair, a medical officer in the Division of Pulmonary, Allergy, and Rheumatology. I'm also a practicing rheumatologist. I will present the safety of baricitinib in rheumatoid arthritis.

Baricitinib is a JAK inhibitor and the safety profile for baricitinib is consistent with the safety profile of a potent immunosuppressant associated with the development of serious and
fatal infections, tuberculosis, herpes zoster, and opportunistic infections, malignancies, and changes from baseline in laboratory parameters, many of which are dose dependent.

Additionally, arterial and venous thromboses were observed in association with baricitinib treatment in the RA clinical program. While many of the adverse reactions listed are typical for immunosuppressive therapy used for RA patients, the dose-dependent platelet elevations and reports of thrombotic events are noteworthy.

In my safety presentation, I will focus on major adverse events, including deaths, serious adverse events, and additional adverse events of special interest.

Among the adverse events of special interest, I will discuss malignancy, serious infections, herpes zoster, opportunistic infections, tuberculosis, major adverse cardiovascular events, overall thrombosis, arterial thrombosis, and venous thrombosis.

I will also discuss laboratory parameters,
including hematologic parameters with a focus on platelet elevations, liver function tests, and lipid parameters. As highlighted in the FDA opening remarks by Dr. Nikolov, safety data analysis was challenging due to the design of the baricitinib clinical program.

The amount of pre-escape placebo-controlled data was limited to 16 weeks. Further, because baricitinib, 4 milligrams once daily, was targeted as the to-be-marketed dose, exposure to the 2-milligram once-daily dose was limited, making interpretation of imbalance in adverse reactions between treatment groups problematic.

Of the 7 phase 2 and 3 studies in rheumatoid arthritis, the 4-milligram dose was studied in all 7 studies, but the 2-milligram dose was limited to 4 of the studies, including only 2 in the phase 3 program.

Patient escapes and crossovers were designed to shift patients who were on 2 milligrams of baricitinib or placebo onto 4 milligrams of baricitinib and added additional complexity to the
safety analyses.

Patients who met escape criteria in the 4-milligram baricitinib group remained on 4 milligrams of baricitinib. In study JADY, patients who met a pre-defined response and were taking 4 milligrams of baricitinib were eligible to be randomized to either 2 milligrams or 4 milligrams of baricitinib.

To further illustrate the complexity of the study design, this slide shows the schematic for the phase 3 studies that included both baricitinib, 2-milligram and 4-milligram, doses. Those are studies JADX and JADW.

For efficacy, the primary endpoint was assessed at week 12 and all patients remained in the study arm that they were assigned to at randomization.

However, at week 16, escapes were allowed in the 2-milligram and placebo groups. Patients who escaped were placed on 4 milligrams of baricitinib. For the 4-milligram group, patients who met escape criteria remained on the 4-milligram dose of
baricitinib.

One of the limitations that resulted due to this design was that patients who had more active disease and were at potentially higher risk of adverse outcomes were escaping to the 4-milligram baricitinib dose, which could bias the safety analyses against that dose.

This designed introduced additional complexity in the analysis of the safety data. In some of the analysis methods described in the FDA briefing document, once a patient escaped to a different treatment, the remaining safety data was censored.

In other analysis methods, the remaining safety data was accounted for, but adverse events were attributed to the treatment the patient was taking at the time of the event. In most cases, this resulted in many events being attributed to the 4 milligrams of baricitinib, even if the patient had initially been randomized to a different treatment arm, potentially biasing the results.
To address some of the limitations highlighted, the agency used several strategies to combine the safety data from the baricitinib RA clinical program. In this table, I summarize the key datasets used for these analyses.

The datasets submitted by the applicant are shown on the left and the additional datasets requested by the FDA during the review cycle are shown on the right. The bottom two rows provide the patient numbers and exposure in patient years for each of the datasets.

In the next few slides, I will outline the strengths and limitations of each of the key datasets used for the analyses of safety and adverse events in the baricitinib rheumatoid arthritis program. The applicants' all bari RA analysis accounting for all patients who were exposed to any baricitinib dose in the RA program.

Although a large amount of exposure data was available with this analysis, this dataset did not allow to make comparisons to placebo or by dose. Further analyses by dose would have had to account
for dose switches. Additionally, doses that were not sought for approval were included in this pool of patients.

The Lilly extended analysis included only phase 2 and phase 3 studies, which included both 2-milligram and 4-milligram dose arms. The exposure time in the treatment arm was censored at the time of dose change, so all adverse events were counted in the treatment arm that the patient was originally randomized.

This allowed for a more accurate comparison between the 2-milligram and 4-milligram doses. However, the approach resulted in a small exposure by treatment arm, limiting the assessment of rare events of interest.

The analysis used in the division director review was from an information request during the first review cycle. The exposure to baricitinib was large, as all four phase 3 studies were included in the analysis. Phase 2 studies were not included, which had further exposure data for both the 2-milligram and 4-milligram doses.
Events were captured after dose switch and attributed to the treatment the patient was on at the time of event. This resulted in a larger amount of the safety data collected, but also attributed events to the treatment dose the patient was receiving at the time of event and not the arm to which the patient was originally randomized.

The CDTL memo used an additional analysis that was requested by the FDA during the first review cycle. This analysis included additional placebo and 4-milligram baricitinib dose exposure from one additional phase 2 study and one additional phase 3 study when compared to the applicant's analysis.

The analysis had elements of the Lilly analysis and the division director analysis. All baricitinib treatment arms included in the analysis had a corresponding placebo arm included. However, one phase 2 and one phase 3 study included did not have a corresponding 2-milligram dose arm.

While each analysis used a different pool of patients and different analysis methods to
attribute adverse events, in general, the safety conclusions were similar regardless of the safety analysis used.

For the purpose of this presentation, the tables in the following slides will present analyses of adverse events using the methods from the CDTL memo for both the placebo comparisons and the comparisons between the 2-milligram and 4-milligram baricitinib doses.

The data in the next slides will be presented using the following time intervals, 0 to 16 weeks to provide the most reliable comparisons to placebo prior to the protocol-specific escape, 0 to 52 weeks for long-term comparisons of adverse events between the two treatment baricitinib doses.

The greater-than-52-weeks data provides the incidence of adverse events with long latency for patients who remained on 2 milligrams or 4 milligrams of baricitinib in this analysis.

The tables to present the adverse events in the baricitinib rheumatoid arthritis program will follow the format shown. For the 0- to 16-week
data, person-year exposure, the number of patients who had the adverse event, and the rate per 100 patient-years will be displayed for placebo, 2 milligrams of baricitinib, 4 milligrams of baricitinib, and patients on 2 and/or 4 milligrams of baricitinib.

Comparisons between baricitinib and placebo will be displayed and comparisons between the 2-milligram and 4-milligram dose will be displayed. Comparisons will also be shown as incidence rate difference, with the 95 percent confidence interval to provide further context about the level of uncertainty around the point estimates.

Placebo exposure was limited to primarily the first 16 weeks of the studies and, for 0 to 52 weeks and greater than 52 weeks data, no placebo data are presented. The primary comparisons for these time periods are between the 2-milligram and 4-milligram doses of baricitinib.

Incidence rate differences with 95 percent confidence intervals will be presented to provide further context about the level of uncertainty.
around the point estimates for the comparisons between the 2-milligram and 4-milligram doses.

The total patient-year exposure for this analysis are shown in the table. As noted earlier in the FDA presentation, the clinical program focused on the 4-milligram dose as the targeted to-be-marketed dose of baricitinib, which resulted in a significantly lower safety database for the 2-milligram dose for all time intervals, as summarized in this slide.

The overall number of deaths was small and was balanced between placebo and baricitinib in the first 16 weeks. The incidence rate for deaths in patients who were on baricitinib at weeks 0 to 52 and beyond week 52 was roughly 0.3 events per 100 patient years and appeared to remain stable with longer exposures.

Serious adverse events are displayed in the next table. Again, from week 0 to 16, serious adverse events are balanced in the placebo group versus the baricitinib-treated groups. Beyond week 52, more events appeared to accrue at a higher rate.
in the 4-milligram dose group compared with the 2-milligram group, but this trend was not consistent with the data from the week 0 to 52 period.

Malignancies, excluding non-melanoma skin cancer, are presented in this table. No malignancies were observed in the first 16 weeks of the placebo group. Malignancies occurred in both the 2-milligram and 4-milligram dose group. The rate of malignancies appeared similar between the two dose groups over time.

Serious infections were noted in all treatment groups and were balanced at week 16 between the placebo and baricitinib groups. The incidence rate of serious infections per 100 patient-years was roughly 3 to 4 and appeared generally similar between the two baricitinib doses.

Herpes zoster occurred significantly more frequently in the baricitinib treatment groups as compared to placebo during the first 16 weeks of treatment. The incidence rate of herpes zoster infections was roughly 3.5 to 4.5 patients with an
event per 100 patient-years, as compared to 1 event in placebo.

No clear dose difference was noted between the 2-milligram and 4-milligram doses for the 0- to 52-week time period. However, beyond week 52, more events appeared to accrue in the 4-milligram baricitinib dose group.

This table shows the opportunistic infections that occurred in the baricitinib rheumatoid arthritis program. In this table, events of multidermatomal herpes zoster were included as opportunistic infections.

In the 16-week period, baricitinib and placebo had similar rates of opportunistic infections. A numerically higher rate of opportunistic infections occurred in the 4-milligram group versus the 2-milligram group, both 0 to 52 weeks and beyond 52 weeks.

This table shows the tuberculosis infections that occurred in the baricitinib rheumatoid arthritis program. In the 16-week period, there were no events of tuberculosis. Most of the events
of tuberculosis were noted in the latter portion of the studies, with events occurring only in the 4-milligram dose group.

Adjudicated major adverse cardiovascular events are presented in this table. In the first 16 weeks, there were comparable rates of MACE between placebo and baricitinib. The incidence rate of MACE was generally similar between the two doses of baricitinib at later time points.

As already highlighted in the FDA opening remarks, arterial and venous thrombosis were observe in association with baricitinib treatment, suggesting a safety signal which was one of the deficiencies cited in the complete response letter.

This slide summarizes the overall thrombosis adverse events and corresponding incidence rates. Of note, most of the events occurred in the baricitinib groups in a dose-dependent manner when compared to placebo. Events of overall thrombosis continued to accrue with continued exposure to baricitinib at a rate of approximately 1 patient having an event per 100 patient-years.
To further characterize the thrombotic events, arterial and venous events were reviewed separately. Arterial thrombosis is a relatively unusual event and appeared to accrue throughout the baricitinib clinical program.

The rate of arterial thrombosis was numerically higher for the baricitinib group versus placebo in the 16-week period. Events continued to accrue and beyond 52 weeks. Events occurred only in the baricitinib 4-milligram group.

Venous thrombosis was a major safety concern during review of the original submission. Events were higher in the baricitinib group as compared to placebo during the first 16 weeks. The rate of DVTs and PEs occurred at a numerically higher rate in the 4-milligram group versus the 2-milligram group. The incidence rate of venous thrombosis was approximately 0.5 to 1 patient with an event every 100 patient-years. In the applicant's resubmission, the applicant provided analyses from observational databases to compare rates of venous thrombosis in patients with rheumatoid arthritis.
and various DMARDs with the clinical data in the baricitinib RA program.

Dr. Sansing-Foster will provide a summary of the data provided by the applicant and additional conclusions regarding the comparison of the clinical data from the baricitinib RA program with the observational data.

Concomitant methotrexate was described as an additional risk of venous thrombosis in the submission. However, I note that many of the patients who were on placebo were also taking concomitant methotrexate.

Safety from the active comparator arms, adalimumab in study JADV, and methotrexate in JADZ were not included in the integrated analyses of safety.

Therefore, for completeness, this slide provides an overview of the safety comparisons, including adalimumab, from study JADV. The results to week 24 are shown in the table. Of note, the rate of serious infections was numerically lower in the adalimumab group as compared with placebo and
baricitinib.

In general, adverse events occurred at a numerically lower rate in the adalimumab when compared to baricitinib, although the number of events in this study were small.

This table provides an overview of safety at week 24 from study JADZ. In this study, patients who were naïve to methotrexate were placed on either methotrexate monotherapy, baricitinib monotherapy, or the combination of baricitinib and methotrexate.

In general, there were numerically higher adverse events with the combination of baricitinib and methotrexate versus either methotrexate or baricitinib monotherapy, including discontinuations, serious infections, and malignancy.

This portion of the safety presentation will present laboratory abnormalities. Hematologic abnormalities were seen with the use of baricitinib. 0- to 16-week data is shown from the pooled phase 3 studies. The hematologic changes
shown indicate a difference from baseline to week 16.

Hemoglobin changes were relatively similar to placebo, with a similar drop in hemoglobin. Neutrophil counts decreased in a dose-dependent fashion and lymphocyte counts increased.

As noted, in the original reviews, baricitinib use was also associated with dose-dependent platelet elevations, which appear unique to this product and deserve further consideration.

The mean platelet counts increase for both baricitinib treatment groups compared to placebo. While the magnitude of increase at week 16 did not appear significant, this table does not capture the significant changes occurring at earlier time points, as shown in the next slide.

This figure shows the mean platelet count change from baseline through week 24 in JADW and JADX, the two phase 3 studies that included both a 2-milligram and 4-milligram dose arm.

As can be seen here, the mean platelet counts were higher in baricitinib treatment groups.
versus placebo, with peak elevations occurring at
approximately two weeks post-treatment in
initiation and the mean levels remain higher than
placebo during the controlled period.

The magnitude of maximal platelet elevation
was approximately 40,000 to 60,000 and was dose
dependent. Following the zenith of the platelet
elevation, the mean platelet counts decreased,
consistent with the anti-inflammatory effect of
treatment, but remained elevated compared to
baseline in a dose-dependent manner.

This dose-dependent effect was also seen at
different thresholds of platelet elevations.
Patients who had platelet counts exceeding the
threshold at baseline were excluded.

The dose-dependent platelet elevations were
seen across the wider spectrum of doses tested in
the phase 2 program, as shown in this slide. This
slide shows the maximum change from baseline in
platelet count for the three phase 2 studies, JADC,
JADA, and JADN, over 13 weeks. With increase in
dose of baricitinib, there is an increase in the

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maximum platelet count.

As platelet elevations were a consistent finding of the baricitinib program, FDA considered a plausible machine related to JAK inhibition and platelet elevations, which will be discussed in further detail by the next FDA speaker, Dr. Whittaker.

Lipid parameters also increased with the use of baricitinib. The increases in lipids appeared to be dose dependent but did not appear to lead to an increased incidence rate of MACE. Liver tests also increased with the use of baricitinib. Changes in AST and ALT appeared to be dose dependent. Cases suggestive of drug-induced liver injury were identified in the original submission and additional information was requested from the applicant regarding these cases in the Complainant response letter.

The additional information supplied by the applicant was reviewed by FDA hepatology consult team, who concluded that there were no cases with biochemical criteria, consistent with Hy's law,
that are causally linked to baricitinib exposure. In each of these cases, a more likely alternative explanation of liver injury had been demonstrated. In general, the safety profile of baricitinib in RA was consistent with that of a potent immunosuppressive. Serious infections, including opportunistic infections and tuberculosis, were observed in the baricitinib clinical trials.

Herpes zoster infections occurred at a higher rate than placebo. Several events of malignancy were also reported. While many of the adverse reactions listed are typical for immunosuppressive therapy for rheumatoid arthritis patients, the dose-dependent platelet elevations and reports of thrombotic events, both arterial and venous, are noteworthy.

Laboratory abnormalities were often dose dependent with the findings of increased platelet counts the most notable. Next, Dr. Whittaker will provide a summary on possible mechanisms of platelet increase due to the mechanism of action of

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baricitinib.

This will be followed by Dr. Sansing-Foster, who will provide the FDA assessment regarding the observational data comparing the background risk of venous thrombosis in rheumatoid arthritis baricitinib clinical program.

This concludes the safety presentation.

Thank you.

**FDA Presentation – Matthew Whittaker**

DR. WHITTAKER: Good morning. My name is Matthew Whittaker. I am a non-clinical reviewer in the Division of Pulmonary, Allergy, and Rheumatology Products.

My presentation today is intended to describe our current thinking as it relates to the potential biologic mechanisms that might explain the clinical observations of increased platelets in patients treated with baricitinib.

Our thinking is informed by evidence from the relevant published literature related to the role of Janus kinase enzyme function in platelet homeostasis. Baricitinib has been developed to
disrupt pro-inflammatory cytokine signaling processes implicated in the pathogenesis of RA.

Generally speaking, cytokines are low-molecular-weight protein or [indiscernible] protein-signaling molecules that are key mediators of the inflammatory response. Their biological activity is transduced through their binding to specific cytokine receptors expressed on the surface of immune cells.

Cytokine receptors are comprised of two or more subunits. They lack intrinsic enzymatic activity and the intracellular portions of class 1 and class 2 cytokine receptors are associated with Janus kinase enzymes, which is shown in purple.

The JAK family of tyrosine kinases is comprised of four enzymes named JAK1, JAK2, JAK3, and TYK2, that act as the signal transduction mechanism for cytokine receptor activation.

Ligand binding to the cytokine receptor induces conformational changes that result in activation of JAK activity. JAK activation leads to three types of phosphorylation events; one,
autophosphorylation and subsequent increased kinase activity; two, phosphorylation of the intracellular portion of the cytokine receptor, resulting in recruitment of signal transducers and activators of transcription or STAT proteins to the receptor; and three, phosphorylation and activation of STATs by JAKs.

Upon phosphorylation, STATs are released from the receptor and subsequently dimerized with other STAT molecules. STAT dimers then travel to the nucleus and function as transcription factors for target genes associated with the inflammatory response.

Baricitinib transiently occupies the ATP binding pocket of JAK enzymes, with the intention to inhibit JAK phosphorylation of STAT proteins, thereby limiting the inflammatory processes mediated through this pathway.

As mentioned previously, there are four different types of JAK enzymes that associate with cytokine receptor subunits; JAK1, JAK2, JAK3, and TYK2. Baricitinib was designed to preferentially
inhibit JAK1, JAK2, and TYK2, while sparing JAK3 inhibition.

The rationale for this selectivity profile is that retaining JAK3 function may reduce the immunosuppressive effects associated with pan-JAK inhibition.

The intended selectivity was demonstrated in cell-free assays that examine the inhibitory function of baricitinib at each isolated JAK enzyme. Baricitinib inhibited JAK1, JAK2, and TYK2 with low nanomolar potency while inhibitory potency at JAK3 was reported to be greater than 400 nanomolar.

Baricitinib was also tested in cell-based assays using human peripheral blood mononuclear cells. These assays tested the ability of baricitinib to inhibit the function of defined JAK enzyme pairs.

The assays measured STAT phosphorylation induced by cytokines that are known to act via established JAK enzyme pairs.

Despite its sparing of JAK3 in isolated
enzyme assays, baricitinib inhibited JAK1-JAK3 enzyme pair function to a comparable extent as to all the other enzyme pairs tested. But it is notable the comparable experiments were carried out with baricitinib and other small molecule JAK inhibitors by an independent laboratory and the results were published in a 2014 paper.

The baricitinib inhibitory potency and selectivity values in cell-free assays were comparable to those reported by Eli Lilly. Interestingly, cell-based assays conducted in human whole blood determined that baricitinib did indeed have a preference for JAK1, JAK2, and decreased inhibitory potency at JAK1-JAK3 relative to the other enzyme pairs that were tested.

This plot of mean change in platelet count from baseline over time in RA patients was shown earlier and it's worth showing again to highlight the time course of platelet increase in patients treated with baricitinib.

The placebo group is shown in the blue trace while the 2- and 4-milligram baricitinib groups are
shown in red and green respectively. There is a peak at 14 days after initiation of treatment, which then returns toward baseline by four weeks, but remains elevated relative to placebo out to 24 weeks.

To understand how baricitinib might be influencing platelet number, we need to discuss the biology of platelet production in the bone marrow in a process that is called megakaryopoiesis.

The key driver in the production of platelets is thrombopoietin or TPO. This is a glycoprotein that is produced mainly in the liver. TPO acts at a receptor known as the myeloproliferative protein or Mpl to direct the expansion and differentiation of hematopoietic stem cells to megakaryocyte progenitor cells, and to megakaryocytes.

Megakaryocytes then shed platelets into the bloodstream. Mpl is a homodimeric receptor and, importantly, in the context of baricitinib, each subunit of a TPO receptor associates with JAK2.

There were two papers published in 2014,
Meyer, et al. in the journal Blood and Ng, et al. in PNAS, that were central to our thinking as it relates to the influence of baricitinib on platelet number.

Meyer, et al. generated mice in which JAK2 was conditionally knocked out in mature megakaryocytes and platelets, but JAK2 function was maintained in more proximal stem and progenitor cell populations.

These animals developed thrombocytosis. Comparable findings were observed in the Ng, et al. paper in which Mpl was knocked out in mature megakaryocytes and platelets, but retained in stem and progenitor cells.

These findings defined two distinct functions for Mpl, in stem and progenitor cell populations versus in mature megakaryocytes and platelets, which are illustrated in this schematic figure.

In this figure, TPO is represented by blue circles, platelets by gray circles, and JAK2 by orange squares. The liver produces TPO, which
travels through blood vessels to the bone marrow.

TPO binds to Mpl expressed on stem and megakaryocyte progenitor cells, stimulating their expansion via JAK2-dependent signaling mechanisms, eventually leading to the production of differentiated megakaryocytes, which deliver platelets into the bloodstream.

The function of Mpl expressed on differentiated megakaryocytes and platelets is to bind circulating TPO, internalize it, and degrade it via a JAK2-dependent mechanism. In both animal models, the loss of Mpl or JAK2 function in differentiated megakaryocytes and platelets resulted in elevated circulating TPO levels.

The increased available TPO in the bone marrow led to increased expansion of the stem and progenitor cell population and ultimately to thrombocytosis. With this understanding of the mechanisms' underlying platelet homeostasis, we asked the question of how might baricitinib increase platelets in RA patients.

So our current thinking is that, at clinical
doses, baricitinib may have more profound inhibitory effects on JAK2-mediated removal of TPO by platelets than it does on JAK2-mediated signaling in stem and progenitor cell populations.

So under these conditions, circulating TPO levels would be increased. The increased available TPO in the bone marrow can stimulate the expansion of those stem and progenitor cells that retain their Mpl function, which would ultimately result in an increase in the platelet population.

As we saw in the plot of mean change in platelets over time in RA patients treated with baricitinib, platelet counts increased sharply during the first two weeks of baricitinib treatment.

We hypothesized that, at clinical doses, baricitinib is present at a concentration that is sufficient to inhibit Mpl-mediated TPO clearance by platelets, but is not sufficient to completely inhibit Mpl-mediated signal transduction in stem and progenitor cells in the bone marrow.

The increased available TPO could stimulate
the expansion of the stem and progenitor cell population and ultimately result in increased platelet production. During the time period from 2 to 8 weeks of treatment, platelet counts returned toward baseline levels.

It is our hypothesis that the now-increased platelet population will be sufficient to overcome the inhibitory effect of baricitinib on TPO removal by platelets. Circulating TPO levels could subsequently decline and the stimulus for platelet production would be attenuated.

Platelet production would be reduced and a new equilibrium would be established. The evidence has shown that platelet counts are elevated chronically in baricitinib-treated patients relative to placebo.

It's plausible that circulating TPO levels are chronically elevated via baricitinib inhibition of Mpl-associated JAK2 in platelets and that the baricitinib levels achieved in the bone marrow are not sufficient to completely mitigate the effects of elevated TPO on the stem and progenitor cell
population.

To summarize, we have used evidence from the published literature to define a theoretical mechanistic framework for the observed baricitinib-induced increase in platelet counts in RA patients.

The key elements of this framework are, one, the extent of platelet production is defined by TPO activation of Mpl in stem and progenitor cells in the bone marrow. Second, circulating TPO levels are controlled by Mpl-mediated removal in differentiated megakaryocytes and platelets. Third and importantly, the biologic function of Mpl is mediated by the activity of JAK2.

Therefore, baricitinib is capable of altering platelet homeostasis via its inhibition of JAK2 associated with Mpl. Specifically, differential inhibition of JAK2 associated with Mpl expressed in mature megakaryocytes and platelets relative to Mpl-associated JAK2 in stem and progenitor cells could enhance platelet production.

With that being said, baricitinib effects on biological processes associated with platelet

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removal cannot be ruled out at this time.

Thank you very much for your attention and Dr. Sansing-Foster will present next.

**FDA Presentation – Veronica Sansing-Foster**

DR. SANSING-FOSTER: Good morning. I’m Dr. Veronica Sansing-Foster and I will be presenting the epidemiology safety study review for baricitinib.

In January 2016, the applicant submitted the new drug application for baricitinib during a 24-week randomized placebo-controlled period of the phase 2 and 3 studies. 6 patients treated with baricitinib, 4 milligrams, reported VTE events, including deep vein thrombosis and pulmonary embolism. Within this period, no thrombotic events were seen within the 2-milligram baricitinib and placebo arms.

In April 2017, FDA issued a complete response letter due to an unfavorable benefit-risk, given the potential risk of thrombosis. December 2017, in response to the complete response letter, the applicant resubmitted the application with the
pooled incidence rates from all patients exposed to baricitinib within phase 2 and 3 clinical trials, herein referred to as the all bari RA population.

I will now describe the details of this observational study. To further address the imbalance in thrombotic events seen in the baricitinib RA program, the applicant conducted a retrospective observational descriptive study. The applicant used data from the IMEDS program within FDA's Sentinel system and the Truven MarketScan Commercial Claims and Encounters database, which also contains Medicare data.

For study inclusion, patients had to have at least 12 months of continuous enrollment within the programs and were required to have 2 rheumatoid arthritis diagnoses, be age 18 or older, and have no diagnosis of a thrombotic event one year prior to or on the index date.

The exposures of interest were conventional synthetic DMARDs, including methotrexate and biologic DMARDs. The outcomes of interest were VTE, deep vein thrombosis, and pulmonary embolism.
as identified by 2 or more diagnoses codes within the inpatient, outpatient, or ambulatory settings with and without anticoagulant use.

Patients were censored at the outcome of interest, death, planned disenrollment, drug discontinuation, the commencement of another medication, or the end of the study in 2015. For the analysis, the applicant compared the crude incidence rates per 100 patient-years to the pooled incidence rates from the phase 2 and 3 clinical trials.

The analyses were stratified by age, calendar year, and gender, although the applicant only provided the rate stratified by age. These are the results from the baricitinib-exposed patients within the all bari RA population and the DMARD-exposed patients from the IMEDS dataset and the Truven dataset.

Rates for both conventional synthetic DMARDs and biologic DMARDs are presented collectively. The various definitions used within the Truven dataset are presented from the most specific
definition, number one, to the most sensitive, definition three.

The VTE rates for baricitinib patients was 0.53 per 100 patient-years while the rates for DMARD patients range from 0.68 to 1.34 per 100 patient-years. Examined individually, the DVT rate for the baricitinib patients was 0.38 per 100 patient-years. The rates for DMARD users ranged from 0.55 to 1.97 per 100 patient-years based on the outcome definition.

Finally, the pulmonary embolism rate for baricitinib patients was 0.24 per 100 patient-years. The rates for DMARD users ranged from 0.26 to 0.77 per 100 patient-years based on the outcome definition.

The applicant concluded that the thrombotic event rates among baricitinib patients were lower than or within the lower range of the thrombotic events observed within the rheumatoid arthritis patients population treated with DMARDs.

Furthermore, the age-stratified incidence rates and rates stratified by conventional
synthetic and biologic DMARD use did not alter the study's conclusions.

In the appropriate setting, FDA might accept IMEDS and Truven's as data source for an observational study. However, to study the comparative safety of baricitinib relative to a treatment alternative such as DMARDs, FDA will require more stringent methods than those used by the applicant.

The overall study designs in the populations compared by the applicant are fundamentally different and aim to address different objectives. In addition, we found the following limitations that preclude comparing the results of the two studies.

First, the patient populations differed. For example, due to differing VTE rates between western and eastern countries, we asked the applicant to stratify the data by U.S. and non-U.S. sites.

However, due to differences in the overall study methodologies, the crude VTE rates from the
U.S. clinical trials could not be compared to the crude rates from the U.S. observational data.

Second, the inclusion and exclusion criteria differed between the clinical trial and the observational study. The data collection methods from medical history, rheumatoid arthritis information, and baseline drug exposure differed between the clinical trials and the observational study.

Fourth, all data sources included patients with current anticoagulant use, potentially for the treatment of a prior thrombotic event. The thrombotic rates are stratified by baseline anticoagulant exposure.

However, due to differences in ascertainment of the drug exposure between the clinical trials and the observational studies, the stratified thrombotic event rates could not even be prepared.

In conclusion, the VTE rates from the baricitinib clinical trials should not be compared to those of DMARD users in the IMEDS/Truven dataset to conclude that baricitinib is less safe, as safe,
or safer than DMARDs.

I will now return the podium to Dr. Raj Nair.

**FDA Presentation – Raj Nair**

DR. NAIR: I will now discuss risk-benefit considerations to conclude my presentation. There are several benefits to the use of baricitinib in rheumatoid arthritis. These include improvements in the two core domains of signs and symptoms of rheumatoid arthritis as well as physical function improvement in patients who take baricitinib versus placebo.

This was reflected in ACR responses and other measures of clinical response as well as improvement in HAQ-DI, as described by Dr. Abugov. In studies that included both doses of baricitinib, the data were not consistent in showing a benefit of 4 milligram over the 2-milligram dose.

Based primarily on integrated efficacy analyses, there is likely a difference between both doses, but that difference if true is likely small. The data on structural progression assessed by
radiographic response showed consistent efficacy for the baricitinib 4-milligram dose.

However, only 1 study evaluated the impact of baricitinib, 2 milligrams, on radiographic progression and it was as an exploratory endpoint. The data from the single trial were not as robust for baricitinib, 2 milligrams, and corroborating evidence from another study was not available.

The FDA review identified a safety profile of baricitinib consistent with that of a potent immunosuppressant with major safety risks of serious and sometimes fatal infections, including opportunistic infections and tuberculosis, malignancy, laboratory abnormalities, increase in platelet counts, decrease in neutrophil counts, and increases in lipid parameters, liver function tests, among others.

While many of the adverse reactions are typical for immunosuppressive therapy used for rheumatoid arthritis patients, such as serious and opportunistic infections and malignancies, the dose-dependent platelet elevations and reports of
thrombotic events are noteworthy.

Further, the assessment of safety was impacted by the design of the baricitinib program, with limited placebo-controlled data and limited safety database with the 2-milligram baricitinib dose.

In summary, while the efficacy data are consistent with the treatment effect of baricitinib versus placebo in the core domains of signs and symptoms and physical function, the results from individual studies were not consistent of a meaningful benefit of baricitinib, 4 milligrams, over 2 milligrams, once-daily dose.

Further, while the data supporting the radiographic response are robust for baricitinib, 4 milligrams, there is some uncertainty about this effect for the 2-milligram dose, which was studied in only 1 phase 3 study as one of the exploratory endpoints.

Risks are consistent with an immunosuppressant and include serious infections, herpes zoster, opportunistic CNS, and tuberculosis.
Malignancies were observed in the clinical trials. Importantly, thrombotic events were noted to be different in the baricitinib-treated patients versus placebo in the placebo-controlled period and continued to accrue throughout the baricitinib development program.

Laboratory abnormalities were also seen, including dose-dependent changes in labs, with the platelet increases being the most striking change, with use of baricitinib suggesting a dose-dependent pharmacodynamic effect of baricitinib.

The agency is looking forward to the scientific discussion and recommendations of the panel members in light of the considerations on the benefit and the risks identified in the baricitinib program in rheumatoid arthritis.

This concludes my presentation. Thank you. At this time, I will turn the microphone back to Dr. Scher.

Clarifying Questions

DR. SCHER: Many thanks to the FDA and everybody that just presented, very clear. So now,
we will open the panel for any clarifying questions for the FDA. And again, please remember to state your name as you're being recorded. We'll begin with Dr. Miller.

DR. MILLER: I have a question for Dr. Whittaker. As far as I know, tofacitinib has not been associated with thrombosis, but is that because tofacitinib has less effect on JAK2?

DR. WHITTAKER: Yes. This is Matt Whittaker. I don't know if we can definitively answer that, but that would be one hypothesis. Tofacitinib does have a decreased inhibitory potency in isolated enzymes at JAK2 relative to baricitinib and is about ten- or twelvefold lower.

There could be other considerations related to the balance of, at least in our opinion, how things are working. It could be other considerations related to the balance between increasing TPO, circulating TPO levels, and inhibiting JAK2 associated with the Mpl in the stem and progenitor cell populations.

DR. SCHER: Can I add to that question?
Because there has been a recent paper looking at the FDA post-marketing surveillance and this is just quoting from -- it's called Drug Safety. That's the journal's name. It's 2018 and it has been published by Abril Verden, et al. And they conclude that the thromboembolic adverse events in the tofa post-marketing program are numerically appearing.

Is there anything that we can add to that point? Are you aware of this?

DR. WHITTAKER: I think I would defer that to clinical colleagues.

DR. NIKOLOV: Yes. I think it's upon us to review that publication that you just referenced to be able to comment more on that. The reviews from the original tofacitinib application are available for public view as well.

DR. SCHER: Thank you. Can I add to that? So the data that's being presented overall in terms of platelet increase is an absolute number. Is there any subgroup analyses or anything that can clarify what the meaning of that absolute increase
is as it relates to the thrombosis events?

In other words, do we start from a baseline
platelet count that's equal at baseline or does
that have any effects on the potential for
thrombosis side effects?

DR. NIKOLOV: So this is Nikolay Nikolov. I
don't think we want to speculate on the association
between the observed elevation in platelet counts
and the thrombotic events. It's certainly notable
and it seems to be unique laboratory abnormalities
among other JAK inhibitors at least described.

We certainly are looking forward to your
discussion and input on both the platelet
elevations and the significance of thrombosis.

DR. SCHER: Thanks, Dr. Nikolov. Next
question is from Dr. Brittain.

DR. BRITTAINE: Yes. My question is about
the statistical presentation. I'm trying to
understand how your presentation of this subgroup
in JADK differed from what we heard earlier from
the sponsor, where they were claiming differences
between, you know, in-treatment effect between the
two subgroups.

Am I correct, because I want to make sure I understand what the differences are, that part of it is that they were focusing on SDAI and you were focusing on other variables? Or can you give me any understanding of why your conclusions seem quite different from the sponsors?

DR. ABUGOV: Thank you. This is Robert Abugov. There is a danger of cherry picking which variables you looked at. Therefore, I chose to look at variables that we consistently look at for inclusion on the label.

I looked at several other categorical variables for interactions such as ACR50, ACR70 as well as HAQ-DI less then various thresholds. SDAI is a categorical variable commonly used to look at low disease activity or remission. I did not find significant interaction effects looking at any of those variables.

I also looked at the confidence intervals between patients with high and low DMARDs in study JADX and did not find any statistically significant
differences.

DR. BRITTAINE: I notice that no one ever looks at ACR as a continuation variable. Is that just not considered relevant?

DR. ABUGOV: I would like to see ACR presented as a continuous variable, although it's not presently done by many of the sponsors.

DR. SCHER: Thank you. Dr. Jonas?

DR. JONAS: Actually, I had a similar question that Erica had. I think this is really actually one of the things that we're really going to have to grapple with, so I want to make sure I understand the differences. Right?

So on the one hand, we looked at slide number C0-40 that the sponsor presented, looking at more refractory patients and showing the statistical difference, particularly for the SDAI. And I realize that's just one variable.

In slide number 22, we looked at multiple other variables that were very different. So maybe you could help us sort of start to think about what these differences are and what they mean or maybe
that's our job to tell you. I guess maybe that's not fair, but putting those two things together, I mean, they're really diametrically opposed in terms of our understanding about whether the 2-milligram or the 4-milligram dose should be the dose that we're going for.

DR. ABUGOV: Right. I think that the results are consistent with a small improvement in response in the 4-milligram compared to the 2-milligram dose. However, the confidence intervals from our integrated analysis suggest that even optimistically the differences are very small and not of minimal clinically important differences.

DR. JONAS: From a clinical perspective, realizing that, in all likelihood, this medication is going to be used for that subset of patients that have failed multiple agents, this is an important question for the committee.

This is not because there are so many other medications that have been previously approved and many of our patients have been through those, and that's why this is important. That's the subset we
really need to be able to grapple with.

DR. SCHER: Dr. Brittain, do you have a clarifying follow-up?

DR. BRITTAIN: Yes. I just wanted to follow up a little bit with that. I mean, we all know that it's difficult to detect interactions. It's harder to detect interactions than just detecting differences between groups. And is that something? Obviously, these studies were not powered to detect interactions. Is that relevant to the consideration?

DR. ABUGOV: I think that is relevant. There could be an interaction. On the other hand, again, the analysis, the exact same analysis applied to patients in that exact same study who had fewer than 2 prior DMARDs, we had a similarly strong signal that the 2-milligram dose was superior to the 4-milligram dose.

I don't believe that's plausible, given what we know about this drug. And I think it cast out on the usefulness of the methodology that the applicant used in patients with 2 or more DMARDs.
DR. SCHER: Thank you. Dr. Katz, just a reminder to state everybody's name before asking the question.

DR. ABUGOV: I was Robert Abegov in that prior answer.

DR. SCHER: Thank you.

DR. KATZ: James Katz. I have a clarifying question for Dr. Nair on his safety talk. I wanted to just better understand the slide about opportunistic infections. That was slide 26 in my booklet. I just wanted to know how the FDA handled, I think it was, six cases of possible PCP. And is that included in this slide, or pneumocystis not PCP?

DR. NAIR: So the question is whether cases of PCP were included in the slide? They should be included as cases in this slide.

DR. KATZ: If I understand correctly, the sponsor reclassified them as not serious and they weren't all adjudicated as pneumocystis. They were just possible.

DR. NIKOLOV: So this is Nikolay Nikolov.
Your question is whether these were included in the numbers in the table? We may need to take a look at that, but we can certainly ask also the applicant for further information on what was and what was not included in these.

DR. McGILL: Dr. Veenhuizen?

DR. VEENHUIZEN: Melissa Veenhuizen, Lilly, global patient safety. All the four cases of PCP were included. As you can see here, three were from Japan. The details of the case relative to what was found in all of those, including the South Korean case, are listed here.

DR. SCHER: Thank you. Does that answer the question, Dr. Katz?

DR. KATZ: My reading was that there was reclassification of cases and I just want to know what impact the reclassification had on the reporting. What if you included suspected cases?

DR. McGILL: Dr. Veenhuizen, could you comment, please?

DR. VEENHUIZEN: Again, Melissa Veenhuizen, Lilly patient safety. We did have discussions with
the FDA on the classifications that they wanted utilized in the submission. And so everything that was put into our submission in that reg response time period and in the resubmission is a line with the FDA's decision, so those cases were included when beta-d-glucan, for example, was positive.

DR. SCHER: Any further clarifying answers from the FDA?

DR. NIKOLOV: Not really. I think we based the numbers off of these information requests received by the applicant.

DR. SCHER: Thank you. Sean Curtis?

DR. CURTIS: Hi, Sean Curtis. I have a question for Dr. Sansing-Foster regarding slide 9 from the FDA. Different patient populations on your slide were cited as a reason why the clinical data cannot be adequately compared to the observational data. Could you just explain that in a little more detail exactly what the hesitation or concern is about that?

DR. SANSING-FOSTER: Yes. When you have different patient populations, you have different
confounders that are not controlled for, so you have different measures of risk. For example, we have the U.S. and the non-U.S. sides. Historically, western countries have a higher rate of venous thromboembolism than eastern countries and the baricitinib study was composed of patients from Japan and from other countries that were not western.

However, the U.S. data was only with the U.S. So it's an unfair comparison because you're dealing with a different background risk from different patient populations to begin with.

DR. CURTIS: If I could just follow up, for example, could not the U.S. data from the development program be compared or pulled out? Would that, for example, be a way to manage that? Or if you could, just explain why that wouldn't be appropriate if that was your conclusion.

DR. SANSING-FOSTER: Dr. Sansing-Foster again. Very good question. We also went a bit further. Within my presentation, I did state, even after they had stratified the rates, the rates were
appropriately about comparable. I think it was .85 to .90.

However, there were differences in study methodologies between the clinical data and the observational data as listed on slides 9, 10, and 11 that still made these rates non-comparable.

For instance, if we go to the next slide, please, thank you, we have past DMARD use within the international sites, but the U.S. site had incident DMARD use. So even if you controlled for looking at the U.S. data only, you still have past DMARD use versus incident use.

Could you please go to the next slide? Then you have drug exposure, which was captured at baseline, versus drug exposure captured three months before baseline. I hope that answered your question.

DR. CURTIS: Thank you.

DR. SANSING-FOSTER: Thank you.

DR. McGUIII: If it would help the committee, we could provide some additional information about that if you would like.
DR. SCHER: Yes. We have limited time, so we probably can --

DR. McGIN: That's fine.

DR. SCHER: -- finish up. So next will be Dr. Setoguchi Iwata.

DR. IWATA: Soko Setoguchi. My question is also related to the efficacy of 2 milligram versus 4 milligram. So looking at slide 15 and 16, it seems to suggest that there are differential effects of 4 milligram versus 2 milligram based on the patient sort of characteristics, so a patient with presumably more severe RA with prior biologic DMARD use seems to have more benefit from 4 milligram compared to those who have only used conventional DMARDs.

Then in going to slide 18, sort of in the integrated analysis, it seems it might not be a good approach to actually combine these two studies with different patients' background. I just wanted to get thoughts on the presenter who presented this slide.

DR. LEVIN: Greg Levin, FDA. So just to
reiterate some of the things that Dr. Abugov said earlier, there are some suggestive differences between the treatment effects, in particular the differences between 2 and 4 milligram, based on these two different subgroups.

To explore whether that heterogeneity would be more than was expected by chance, we ran some interaction tests and those were not convincing of an interaction. They don't rule out an interaction. It could be true. But you do expect a lot of heterogeneity across subgroups just by chance in clinical trials and so we didn't find that evidence convincing.

Furthermore, I think, when we looked at the individual study results and the integrated results, all of them kind of suggest that there might be a small difference between the doses. And if you look within the subgroup with who had taken 2 or more DMARDs, you again see small differences between the doses.

So we didn't think that these kind of post-hoc subgroup analyses fundamentally changed the
conclusions, which ours were, that there's likely some small differences between the doses. And one additional note is, I think there was a question from Dr. Bilker earlier about the safety in these subgroups.

So it would ultimately be a benefit-risk discussion across these different subgroups. And it's a very small safety database in terms of these rare adverse events, even in the overall population. So when we start to break it down by subgroups and talk about comparing 2 versus 4, for example in the subgroup who had taken 2 or more DMARDs, there's a lot of uncertainty there.

So I think talking about benefit-risk in subgroups is even more challenging than talking about benefit-risk in the overall population. And so we didn't find these comparisons within the subgroups particularly convincing in terms of changing conclusions in the overall population.

DR. SCHER: Thank you very much. So we have five more minutes for this aspect of the discussion. We will have way more time in the
afternoon, so I'm going to give time to Dr. Kim
followed by Diane Aronson so we hear from patient
representatives. Dr. Kim?

DR. KIM: Yes. Seoyoung Kim. Going back to
slide 15 of the first presentation by FDA, I was
wondering, for the ACR50, it must be a typo.
Right? 5 percent; is that true? It can't be less
than ACR70. Right? Or is that really 5 percent, 2
percent, 2 percent?

DR. NIKOLOV: It's likely a typo.

Dr. Abugov?

DR. ABUGOV: Yes. This is Robert Abugov.
It's likely a typo. I don't have my computer here
and my statistical analyses, but I think you're
right.

DR. KIM: Then I have more one question
related to this slide. So in the applicant's
presentation, they used SDAI as one of the figure
presentations in CO-40. If we have a slide like
this for all the measured outcomes, I think that
might be even more useful for us to assess, not
just, like, as you said, cherry picking the five
outcomes if we have all the other -- I don't remember the exact number of outcomes. Do you have that kind of data handy?

DR. ABUGOV: I don't have it handy. Yes, I don't have it handy. Thank you.

DR. KIM: Thank you.

DR. SCHER: Ms. Aronson?

DR. ARONSON: Diane Aronson, patient representative. As a patient, we often go right to the label to weigh and evaluate what we're going to do, the choices. And I notice that, on page 164 of the FDA document, there was a discussion about a proposed statement regarding warnings and precautions.

I understand we may not be able to see the label that's going to be put out, but the FDA did state on this page that there was "no clear relationship" to thrombotic events that is being proposed by the sponsor.

That could have been a previous study or because we reviewed a number of points, but I'm just wondering, too, not being clear about
exclusions or I just want to know more. That's all. Thank you.

DR. NIKOLOV: So this is Nikolay Nikolov. I will try to respond to that. So what we included in the briefing document is what was proposed by the applicant for transparency. What will end up potentially in the labeling is still a matter of review.

The statement proposed by the applicant is difficult to support based on the data that we have because any of these associations cannot be ruled out or ruled in. Besides the incidence, besides the elevations in platelet counts, one must also considered whether there might be some functional effects on platelets that might not be measurable by the peripheral platelet counts, but that may still contribute to the mechanism of action.

Again, we want to specifically try to avoid implying platelet elevations in the thrombosis events, but we certainly would welcome discussion on this topic.

DR. SCHER: Very well. I want to thank
everybody again. We're breaking for lunch. We will be reconvening in this room in about an hour at 1:00 p.m. sharp. Please take any personal belongings you may want to keep with you at this time and, committee members, a reminder not to discuss amongst yourselves. Thank you.

(Whereupon, at 11:59 a.m., a lunch recess was taken.)
AFTERNOON SESSION

(12:30 p.m.)

Open Public Hearing

DR. SCHER: Very well. Welcome back. We will now begin the open public hearing session. Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA
encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the 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 me. And thanks for your cooperation.

So we will now begin. 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.

DR. SOTO-RAICES: Hello. There we go. My name is Oscar Soto. I'm a rheumatologist and the medical director of Mindful Rheumatix and Mindful Medical Research Center.

I spend most of my time between clinic and research duties. I also have been involved in patient advocacy since 2009 through the Puerto Rico Foundation for Rheumatic Diseases, where I serve as the president of the board of directors.

I'm here on my own behalf, on behalf of the healthcare providers at our center, and the patients with RA we have seen and continue to follow on different baricitinib clinical trials throughout the years and today.

I have no disclosures to make regarding my travel or compensation for this presentation and I wanted to thank the committee for the opportunity to speak here today. I have worked as an investigator on several trials with JAK inhibitors, including tofacitinib, upadacitinib, and baricitinib.
As you know, baricitinib is an oral reversible inhibitor of JAK1-JAK2 kinases that are involved in mediation of signal transduction for several cytokines that play an important role in the pathophysiology of rheumatoid arthritis.

The complex pathophysiology of RA makes it a disease with many possible presentations and many possible targets. The heterogeneity of the clinical presentation makes it a difficult condition to treat as different patients will respond to different treatment.

Even patients who respond may lose treatment over time. These are some of the reasons that support the need to continue to expand our treatment options for patients with rheumatoid arthritis.

There is a need to continue finding effective treatments with an acceptable and stable safety profile that could be easily stored without the need of refrigeration or without requiring patients to go to a medical facility for administration.
Me, my colleagues, and staff have had the opportunity to follow patients in all baricitinib phase 3 trials. And they are still being followed regularly after rolling over to the ongoing extension of open-label protocol.

Data that has been published and presented at meetings has showed it to improve disease activity and slow down where inhibited radiographic progression in a variety of patients with RA.

These results of the data obtained in this trial is consistent with our experience as we follow individual patients and their daily struggles as they continue their journey to recovery with less joint pain, less swelling, better mobility, less fatigue, and overall improvement of their daily function.

Beyond the data and beyond the statistics, the stories of the patients we have followed on baricitinib clinical trials is what we believe to be the most important thing to convey, as it is likely the most common story.

Again, it goes beyond the numbers and the
way they are analyzed. We have seen a significant improvement in disease activity and function on a regular basis on all kinds of patients, populations studied, and mentioned previously in different trials, but we have seen it on a day-to-day basis.

We have seen a significant improvement in disease activity and function on patients with no exposure to DMARDs in the past, who are struggling to accept a chronic disease that brings pain and possible loss of function.

In those who have failed conventional DMARDs and biologic DMARDs, most importantly, we have seen improvement in patients' well-being as they find hope and foresee a brighter and better future. Patients' stories and their journeys in conjunction with the data that let us know that our experience is one of many and have led me to believe that this is an effective treatment alternative that is well tolerated in a variety of patients with active RA.

It is for all these reasons that we support baricitinib approval as a new alternative for the treatment of RA to help as many patients as
possible achieve a healthier and more productive life. Thank you.

DR. SCHER: Thank you, Dr. Soto. 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. CAROME: Good afternoon. I'm Dr. Michael Carome, director of Public Citizen's Health Research Group. Public Citizen and I have no financial conflicts of interest.

Public Citizen strongly opposes FDA approval of baricitinib for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate because the FDA correctly concluded prior to issuing its April 2017 complete response letter to the sponsor that "the overall benefit-risk assessment of baricitinib, 2 milligrams and 4 milligrams, once daily was not favorable" and the sponsor has not provided any data that substantially alters the agency's conclusion.
We therefore respectfully urge the committee to recommend that FDA not approve the drug. Data submitted from 4 pivotal randomized controlled trials testing baricitinib at doses of 2 or 4 milligrams once daily, in comparison with a placebo or active comparator, did demonstrate efficacy in improving the signs and symptoms of RA as assessed by the ACR20 response and on other measures.

Of note, the two trials that compare baricitinib at 2 milligrams and 4 milligrams once daily did not show consistent separation and efficacy outcomes between the two doses, with the dose response for the primary outcome measure being opposite in the two trials.

Baricitinib causes numerous serious adverse reactions typical of many other potent immunosuppressive drugs, including the following, shown here, which have been discussed in detail already.

However, of great concern as discussed in detail by the FDA, baricitinib appears to have a unique risk of thrombotic events, a risk not seen
with any small molecule or biologic DMARDs.

As shown in this table from the FDA briefing document, analysis of pooled data from baricitinib group and placebo group subjects in the phase 3 clinical trials and their extension in JADY demonstrated that the events reported as deep venous thrombosis and pulmonary embolism were seen only with baricitinib.

FDA review of the initial application revealed that there were 10 PEs reported with baricitinib. 9 of those were serious and 1 was fatal. And there were 10 DVTs reported with the drug. 6 were serious. The initial application also revealed in the phase 3 trials that there were several cases of arterial thrombosis in subjects who received baricitinib, including 2 involving the leg and 1 involving the brachial artery.

Baricitinib also clearly causes an increase in platelet count, an effect that, according to the FDA reviewers, has not been seen with other JAK inhibitors such as tofacitinib for RA or other DMARDs as shown in this figure from the FDA.
briefing packet.

Of note, there was not a clear relationship between the occurrence of thrombotic events and the platelet count elevations. In addition, more subjects receiving baricitinib, 4 milligrams, were discontinued from the drug due to liver enzyme elevations than in all other comparator groups.

I would like to highlight some of the critically important observations made by senior FDA staff regarding the FDA's original benefit-risk assessment for baricitinib based on the sponsor's first application.

Dr. Chowdhury, director of CDER's Division of Pulmonary, Allergy, and Rheumatology Products, prior to the issuance of FDA's complete response letter, noted the following in his benefit-risk assessment of baricitinib.

"The thrombosis findings are of particular concern because these events are not predictable and some were associated with death." As for laboratory parameters, it is worth noting that 2 patients were withdrawn from the studies for
meeting platelet threshold criteria for withdrawal. Both were from baricitinib, 4 milligrams.

Lilly argues the thrombosis risk of comparing the patient population, but comparisons to population data are not relevant because the risk with baricitinib was seen in controlled clinical studies.

On further review and consideration, I now question, if baricitinib 4-milligram dose is not safety, why the lack of safety of the 4-milligram dose would not be applicable to the 2-milligram dose. The safety database of the 2-milligram dose is not large enough to independently assess safety of the 2-milligram dose and compare that to the 4-milligram dose.

Furthermore, the safety finding that is of particular concern is the thrombosis event. The biologic DMARDs in tofacitinib do not have this safety risk. There will need to be further safety data generated to understand the thrombosis risk for baricitinib and it would be reasonable to obtain the data and address this safety risk pre-
It is possible that, in real life, post-
approval use by a wide range of patients with
rheumatoid arthritis, the 2-milligram dose may turn
out to carry the same safety risk that is worrisome
for the 4-milligram dose.

Also, as discussed above, it is possible
that a dose lower than 2-milligram dose may be
effective as well and have a better safety profile.

Given that baricitinib is another member of the
DMARD class that has many choices and baricitinib
is not serving an unmet medical need that is above
and beyond biologic DMARDs and tofacitinib, it
would be reasonable to not approve any of the doses
of baricitinib at this time.

Likewise, the deputy director of CDER's
Office of Drug Evaluation II stated the following
in her benefit-risk assessment prior to issuance of
FDA's complete response letter, "Although the
number of thrombotic events was low, the absolute
number and imbalance to controls during the first
16 weeks of pivotal studies distinguishes
baricitinib from other approved RA therapies, particularly tofacitinib."

Given the infrequency of the thrombotic events of this program, the serious safety concerns associated with other RA therapies, some overlapping with baricitinib, and the efficacy demonstrated with baricitinib, 2 and 4 milligrams in the phase 3 trials, I considered whether a subgroup of patients could be identified where the benefit risk calculus of baricitinib, 4 or 2 milligrams, could be favorable and also provided an advantage over other available therapies.

Identification of such a population might at least allow for an approval limited to a select group of patients. There were two studies in which baricitinib, 4 milligrams, demonstrated superiority over an active comparator. In JADV, baricitinib, 4 milligrams, was superior to adalimumab in RA patients who had an inadequate response to methotrexate.

In JADZ, baricitinib, 4 milligrams, was superior to methotrexate in RA patients naïve to
drug treatment. Despite these findings, I could not justify the risks associated with baricitinib, 4 milligrams, over the active comparator because the currently marketed JAK inhibitor, tofacitinib, had also been shown effective in these two populations, but without the risk of thrombosis.

If it were the first-in-class oral JAK inhibitor, there may be a justifiable basis for carving out a niche population for baricitinib, 2 and 4 milligrams. However, the evidence with tofacitinib in its pre-marketing application and subsequent phase 4 trial since its approval in 2012 was established has established its efficacy in RA patients across a spectrum of disease severity, its efficacy relative to adalimumab and methotrexate, and its ability to reduce radiographic progression.

These are the same populations and endpoints for which baricitinib is seeking approval, however without the concerning thrombotic risk that appears unique to baricitinib. In conclusion, review of this NDA has identified a serious safety risk of thrombosis not observed in other marketing
applications for available RA therapies, especially tofacitinib.

Absent an advantage of baricitinib over available therapies, the applicant will need to explore whether a lower dose can provide efficacy without the safety concern.

In response to the FDA's April 2017 complete response letter, the sponsor resubmitted its NDA in December 2017. To address FDA's concerns, the sponsor submitted the following, among other things: several post hoc analyses and subgroups from the trials, reviewed by the FDA, safety analyses with an updated cut-off date, a comparative analysis of retrospective cohort studies from the Sentinel and Truven MarketScan databases with the prospective baricitinib studies in RA to evaluate venous thromboembolic risk.

Importantly, none of these additional analyses submitted by the sponsor alter the FDA's original unfavorable benefit-risk assessment for the drug. The sponsor also submitted a modified dosing regimen and that the modified dosing regimen
and the thrombotic risk be managed through warnings in the label, communications with health professionals, and routine pharmacovigilance.

Regarding the post hoc analyses that purport to demonstrate superior efficacy of baricitinib, 4-milligram dose over the 2-milligram dose in patients with inadequate response or intolerance to at least 2 DMARDs, the FDA concluded that these analyses should be considered "exploratory and hypothesis generating rather than confirmatory."

Regarding the safety analyses with an updated cut-off date, the updated incidence rates of venous thromboembolic events was .6 per 100 patient-years in the 4-milligram group and .4 per 100 patient-years in the 2-milligram group, which are very similar to the rates reported with the sponsor's initial submission, shown here from the FDA briefing packet.

Finally, regarding the comparative analyses of retrospective cohort studies from the Sentinel and Truven MarketScan databases with the prospective baricitinib studies in RA to evaluate
venous thromboembolic risk, the FDA noted in its review the following.

The VTE rates from the baricitinib clinical trials should not be compared to those of DMARD users in the IMEDS/Truven data to conclude that baricitinib is less safe, as safe, or safer than DMARDs. The study designs and populations are fundamentally different, and aim to address different objectives.

The clinical trial incidence rate should not be compared to the observational study incidence rates to assess relative safety for four major reasons. One, the data collection methods for medical history, rheumatoid arthritis information, and baseline drug exposure differed between the clinical trials and the observational studies.

Two, the exclusion and inclusion criteria differed between the clinical trials and the observational studies. Three, the crude VTE rates from the U.S. clinical trials cannot be compared to the rates from U.S. observational data despite similar incidence rates.
Finally, data from the all bari RA IMEDS and Truven included patients with concurrent anticoagulant use, potentially for treatment of a prior VTE.

In summary, the FDA's overall assessment of the addition of data provided by the sponsor in the resubmitted application was that, "It did not substantially alter the efficacy and safety data in the original submission."

In conclusion, given the available data, the only reasonable course of action for this committee and the FDA is to reject approval of the NDA for baricitinib. FDA approval with reliance on warnings in the product labeling and post-market pharmacovigilance would be a reckless approach and would not be in the interests of public health.

Approving another drug for treatment of RA that lacks any unique benefit over the very similar FDA-approved drug tofacitinib, but causes unique life-threatening harm such as venous and arterial thrombotic events which show blatant disregard for the public health principles underlying FDA's
regulatory authority.

Therefore, we respectfully urge the committee to recommend that FDA not approve baricitinib. Thank you.

DR. SCHER: We thank Dr. Carome. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. DiPERI: Good afternoon. My name is Christine DiPeri. Eli Lilly provided my transportation and lodging for this event. Regardless, I would have come for three important reasons, my two children and all the moms with rheumatoid arthritis who don't have an opportunity to speak before this panel about the importance of effective, available treatment.

I have had rheumatoid arthritis for 19 years. And during that time, I've been on multiple treatments, effective for a time. When my health started to fail on Enbrel, I was out of options. I didn't understand how that was possible. What I was left with was methotrexate.
For the audience who may not be aware of this, methotrexate is a chemotherapy medication. I get an injection of it once a week from my care partner, i.e. my husband. I'm not complaining much. As you can imagine, taking a chemo drug weekly is no picnic.

Before the medications failed, I was an active mom, the Den Leader, the PTA president, life partner with my husband of over 25 years. And then I was an invalid, which is why I became a human guinea pig.

I travel 200 miles round trip to see my rheumatologist so I can be in this study. Every three months, I make that trip and I will continue to do so solely for this medication.

Today, thanks to this medication, I can count on getting up in the morning and being able to go to my job. Yes, I now have a job. I'm a supervisor in a call center, a very active position. I wear a Fitbit.

But most importantly, I have a life with my family. I can go shopping and sightseeing with my
husband and do other fun stuff. I did a 5k with my son and I can help my daughter move in and out of college housing. She graduates next month.

A few years ago, I thought she had dandruff or cradle cap. It was my rheumatologist who told me it's psoriasis, which fills me with dread because I know that that's psoriatic arthritis. I don't think she knows the possibilities, but I'm positive that she remembers the months that I lived in the living room of our home in one of those horrible reclines. You know the type. It goes upwards and sort of ejects you out of it, you know, for the people who are 80 years old.

But I wasn't 80 years old. I was 40 years old and I had two children who were suddenly wondering why Mom couldn't move, why Mom wasn't sleeping upstairs with Dad, why Mom was sleeping in the living room; because I couldn't manage to go up the stairs and I couldn't manage to dress myself.

One of those simple things that everyone likes to throw around of morning stiffness; it would take me 20 minutes to walk from this podium
to that suitcase with morning stiffness.

Now, I can probably do that in a matter of seconds. And I use an enhanced toilet seat because ADA seats just aren't high enough when your knees don't work. Having my husband dress me because my fingers don't work, my whole family; we remember that.

It's not fun to tell your children that you can't sign their school papers because you have 'the claw'. I remember going to my doctor's office for them to draw blood and the nurse said to me, "Make a fist," and I did this. And she said it again. And I said, "I know what the word fist means. This is all I can do."

My fingers work now and I'm grateful. It's hard for children to believe that their mother isn't dying when she's sick every day. A good day is when she has a severe flu and lacks the energy to have a conversation. That's a good day. It's heartbreaking as a parent not to be viable as a person, not to be active in your children's lives.

Medicines fail and I know I have an active
strain of RA. I tested positive for rheumatoid factor and CCP. I implore you to approve this medication. It has sustained me longer than any other and it has enabled me to have a life.

The TV commercials don't tell the story of what rheumatoid arthritis is. It's completely debilitating. It's pain in your joints that brings you to tears.

I am not a professional golfer like Phil Mickelson. I'm just a mom trying to live a life. It's constant exhaustion, agony for your family, which is why this medication is needed. My dose is 4 milligrams. I was rescued to that level and it truly was a rescue because not only is there a physical toll with RA, there is a mental toll.

I am grateful that I can wake up and make it to the bathroom. I can walk up and down stairs during a fire drill at work. I can sit down on the floor and I can actually get up now.

DR. SCHER: Ms. DiPeri, please wrap up.

DR. DiPERI: Better living through pharmaceuticals. That's what my family calls it.
It's my life and I'm grateful to have it. For me and all the RA moms, for the children who will grow to be diagnosed with this disease, I implore you to improve this drug at the 4-milligram dose.

Keep us moving, keep us living. To all the doctors, and analysts, and researchers, thank you.

DR. SCHER: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. PERKINS: Good afternoon. I'm Dr. Elizabeth Perkins, a practicing rheumatologist from Birmingham, Alabama and driven here today on behalf of the patients I treat back home. I have no financial disclosures for today's travel and meeting with you.

There has never been a better time for RA patients to find healing for their disease. Since the advent of a new class of JAK treatments, we are now able to expand our excellent choices to the complex RA cases, the non-responders, and the patients who do not tolerate current treatments.
In private practice in Birmingham, Alabama, I have treated over 1,000 RA patients and what they teach me room to room and day to day is that RA is complex. It is stubborn and it rarely occurs alone. Individual RA patients require thoughtful choices in their mechanism of action and in their route of administration.

Although we talk about studies and large groups and populations in this room, when you're in the room with a patient, it's an N of 1 and their opportunity to find the right drug just for them.

They teach how differently RA presents in different bodies and how frustrating it can be for them to find a treatment that works for them, especially when they're grouped into large groups that don't consider the individual characteristics of their disease and one-fits-all formularies.

Patients teach us it's not just about their joints. It's about the systemic effects of RA inside their body and in the outside world, affecting their jobs, their family members, and their personal lives.
The other missing piece of trial data is how commonly RA occurs with other autoimmune diseases such as overlap with Hashimoto's, lupus, coagulable disorders, Sjogren's, psoriasis, and like she mentioned mood disorders.

Real-life RA patients have strange rashes, gland and lymph node swelling, bowel problems, and most commonly they complain of no energy and hair loss.

They often have co-morbidities and, when they are sitting across from me, we aren't just targeting debilitating joint pain fatigue, deformities, disability, and early cardiovascular disease. We are actually addressing these problems in overlapping conditions with very unique characteristics and health issues in mind.

What I have experienced in clinic is that JAKs have a timely powerful impact in these types of patients. Like you, I have reviewed the clinical data for baricitinib and other JAKs and believe baricitinib has a unique efficacy and tolerability that will close the gap in our
In my clinic, RA patients with these blended autoimmune diseases overlap conditions. They have responded well to JAKs. The JAK responders will tell you that these have changed their life and have been a miracle for them. It is not just about their joints. It's about treating the total patient and the total patient is getting better. With the promise of a new JAK like baricitinib, we will continue to close these treatment gaps. Keep in mind, RA patients don't come to my office asking for a lower CDAI or an ACR60. Rather, their war cry is actually that the medicine we pick together will be safe and work in all aspects of their health. By far, the overarching ethos of their visits is that they will have total wellness and get their lives back. It goes without saying that we rheumatologists must be good stewards of the welfare and safety of our patients and first do no harm. The pressure weighs heavily on us when we
are picking a biologic or a JAK treatment. We know that these diseases are complex. The treatments are complex and require careful toxicity monitoring.

Luckily, in our training and expertise, we get that kind of training and, most recently with the evolving JAK class, we have learned how to do a better job at safety. I am proud that, as a result of the JAK class, we've actually raised the bar in our clinical practice to do a better job of preventing cardiovascular disease, monitoring labs, scouting for infections, and scheduling vaccines proactively.

I know that, as a result of baricitinib's approval, we will continue to enhance our safety practice in the clinical setting. I hope, with the appropriate labeling, like other countries throughout the world, the U.S. patients will have access to baricitinib at the right dose for them. In reality, the severe RA patients waiting for baricitinib's approval in my clinic have higher disease burden and more severe disease. The second
greatest challenge these patients will have after getting the right drug for them will actually be access to the drug.

Thus, my plea to the FDA today will be to --

DR. SCHER: Dr. Perkins, please wrap up.

DR. PERKINS: -- approve a label for baricitinib that will allow patients timely access to the right dose. Higher disease burden can't afford inadequate response rates or delays in their treatment or dosing errors, misguided formulary restrictions by insurance companies. I am grateful for the honor to be a rheumatologist before my government and FDA colleagues today and to advocate for the highest standards of are with you and be a part of this mission, where our --

(Audio interrupted.)

DR. SCHER: Thank you, Dr. Perkins. Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. AOANAN: Good afternoon. My name is Sarah Aoanan. I'm the patient advocate and
community outreach manager for the Global Healthy Living Foundation.

I have no disclosures to make here today.

On behalf of GHLF, 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.

GHLF represents more than 100,000 chronically ill patients and their caregivers across the country. Many of these individuals are a part of our online arthritis community, CreakyJoints. They have rheumatoid arthritis or other related autoimmune diseases and have had their lives changed first from their diagnosis of a disease like RA and then consequently, their lives are restored because of innovative therapies that are today available to them.

Our patient community knows we speak on their behavior to the FDA and they don't hesitate to tell us what they think we ought to say. It's
not unusual for a patient to be a citizen expert on
the drugs they take. We are proud to amplify their
voice and help them engage with a larger audience.

This is why we're here today. The patients
we serve utilize the internet to connect with other
patients around the world to help them navigate an
environment that is often scary and overwhelming.

They're committed to staying informed with
the latest research on autoimmune arthritis and
creating dialogue with others fighting these
diseases. On behalf of this community, we are very
pleased to be here to support an additional
treatment option being added to a class of drugs
that may enhance the quality of life for patients.

We are pleased to see that the medication of
interest today shows greater efficacy than
adalimumab in at least 1 study as well as placebo.
We believe JAK inhibitors such as the one being
discussed today bring great value to patients with
RA because the oral route of administration is a
patient-centered one and may lead to greater
compliance.
People living with autoimmune diseases tell us that medications taken orally are preferred for several reasons. Among them are, A, needle phobia, B, convenience and mobility challenges associated with not having to travel or arrange transportation to an infusion center or doctor's office to receive assistance in using self-injector devices, and C, not needing to worry about special storage, handling, or care instructions.

When we ask our patient community what they'd like us to say to FDA regarding the approval of new therapies such as the one being considered, we often hear a similar message in different ways and from different perspectives.

Patients share experiences, learning to live with pain daily, but also having to cope with frustration or anger of loss of physical independence and their perceived value to their family, work, and society.

They have tried many therapies, some that never worked, some that worked for a short period of time, and some that have caused intolerable side
effects. They learn to become flexible and adapt their lives to different methods of administration. They read safety pamphlets and watch training videos about how to stick themselves with needles or coordinate travel to and from infusion facilities.

Our community members do this all to maintain hope, hope that their next attempt on a new treatment will be the difference and will change their life, hope that, if their next treatment fails, there are additional treatment options under development, ready to replenish the option bank.

Ultimately, we always put our faith and trust in the experts at FDA to ensure that patients have access to safe and effective treatments while taking into consideration the unmet needs of patients impacted by these diseases and balancing risk and benefit.

We respectfully offer our support for this submission. We thank the FDA for emphasizing the value of the patient perspective through public
meetings and we continue to mobilize our patient community to create a better life for those who will benefit from therapies like this one.

Thank you for your time and attention. It's greatly appreciated.

DR. SCHER: Thank you, Ms. Aoanan, and also for being on time. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. MARKSBERRY: Good afternoon, Chairperson and committee members. My name is Denise Marksberry. As you can tell, I am an RA patient. I was diagnosed at the age of 2. Growing up in the '70s, I only had 8 aspirin a day for 10 years. There was nothing available as a child growing up.

Now that the damage is as extensive, myself, I am now running out of options. I'm on the infusion level and there is nothing left for someone like me. And there are millions that are just like me.

We need another option. We shouldn't have
to settle with adverse side effects, not being able
to function. I fight every day to get up, to move
on. I lost my train of thought.

Days when I can't, I am wheelchair bound
while I wait for insurance companies to approve
another medication. It's a fight. I don't walk.
And I am afraid, one day, I'll never walk again
while I wait. And it's so hard because the doctor
has nothing for me left.

So please approve another option for the
millions that suffer with RA every day just like
me, so they don't look like me. Thank you.

**Clarifying Questions (continued)**

DR. SCHER: We thank you very much. The
open public hearing portion of this meeting has 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, the careful consideration
of the data before the committee as well as the
public comments. Dr. Nikolov will now provide us
with a charge to the committee.
I was just reminded that I cut short a couple of questions from the other session by Dr. Bilker followed by Dr. Caplan, and then we will have five minutes for the sponsor to clarify some other aspects of the presentation.

DR. BILKER: Thank you. This is Warren Bilker. I have a question about the -- I think this is for Lilly -- retrospective cohort, the retrospective observational study. In particular, I believe it's retrospective ascertainment.

My concern is the possibility of selection bias of patients who have events after the study is undertaken, because you would go back retrospectively and collect their data. So what I wanted to learn about is, what are the selection criteria for those who enter the study, so I can assess whether there's a potential for selection bias?

DR. McGILL: Dr. Motsko?

DR. MOTSKO: Steven Motsko, epidemiology, Eli Lilly. So are you referring to the currently ongoing post-marketing studies in Europe and Japan
or are you talking about the studies that we're proposing to do once baricitinib is approved in the U.S.?

DR. BILKER: The study you are proposing to do when it's in the U.S.; what are the selection criteria? That was a retrospective study. Right?

DR. MOTSKO: So the primary study will be doing a prospective observational study with 4,000 baricitinib patients compared to a biologic active control. And it will be following those patients over a 8- to 12-year duration, looking at long-term outcomes, but also VTE and thrombosis.

We're talking about the top one up here. We are also proposing a retrospective database.

DR. BILKER: No, it was the retrospective one. That was it, yes.

DR. MOTSKO: Yes. That will complement it, but there will be no inclusion/exclusion criteria. This will be looking at real-world use and observing patients compared to an active control as well.

DR. BILKER: But the data will be
retrospectively ascertained. Right?

    DR. MOTSKO: Sorry. Yes, the data will be
retroactively ascertained, but we will be starting
patients at initiation of the drug and then
following them forward in time, so it's kind of
historical.

    DR. BILKER: So it's prospective. Okay.

Thank you.

    DR. SCHER: Thank you. Dr. Caplan, please?

    DR. CAPLAN: I had just two questions for
clarification. The first is on the Nair slide 29,
which lists the overall thrombosis. This is in the
FDA report, also similar data presented in table 24
in the documents in preparation for the meeting on
page 61.

    It lists 7 thromboses under the baricitinib
4-milligram dose. Every reference outside of this
identifies 6 events. And I think, after I pose
this question, I may have identified the
explanation for why there was this incongruity.

    Is that last event -- and I guess this would
probably be for the sponsors -- from a crossover or
the escape?

DR. McGILL: Let me ask Dr. Baker to answer the question, please.

DR. BAKER: Thank you. I'm Robert Baker from Lilly. I believe what's been done in this agency presentation is to lump together in the same graph both arterial events and venous events.

Lilly's presentation focused on them separately, given different pathophysiology between them. So the 6 number you saw was only for venous thromboembolic events. I believe the seventh one here is an arterial thromboembolism. Again, we didn't want them because the pathophysiology appears different and because, as we looked at the overall placebo dataset that we have between 4 milligrams and placebo.

If you include the adalimumab study, actually, there was no difference in the rate of arterial events between baricitinib and placebo. So the primary question here is about venous events and that's where you've seen the 6. Does that answer your question.
DR. CAPLAN: Yes.

DR. NIKOLOV: Maybe FDA?

DR. SCHER: Yes. Yes.

DR. NIKOLOV: We also have a point of clarification.

DR. NAIR: So this is Raj Nair from FDA. So if you're referring to the overall thromboses tables from the previous reviews, this number is 1 higher because additional DVT was noted in the resubmission that should have been included in the original submission, so that 1 case has been added. So I think that's what the discrepancy is.

DR. CAPLAN: Yes, that's a different explanation. Then with reference to CO-54, I apologize. I may have missed this. If I understand this slide correctly, this is comparing the stepdown, which I know is not one of the major points, but I think it lends some data that might be useful in understanding the difference between the 2 milligram and the 4 milligram.

Am I understanding this correctly, that the blue columns are comparing those that remained on
baricitinib versus those that stepped down in the
gold and that the asterisks indicate that there is
a statistical difference between these two and that
these two groups were in fact randomized? I
apologize for the three-part question.

DR. McGILL: Dr. Rooney?

DR. ROONEY: No worries. Terence Rooney,
Lilly. Thank you. Yes, this was a randomized,
double-blind comparison. In fact, the patients nor
the investigators even knew when randomization was
happening. And your interpretation of the
asterisks is correct.

There was a statistically significant
difference between 4 milligrams staying on and
tapering to 2 milligrams with respect to
maintenance of low disease activity at each of
these time points. And the same observation was
verified in a series of additional pre-specified
analyses, including change from the time of re-
randomization to each of these landmarks in each of
the composite disease activity scores and all of
their components, and then finally a pre-specified
analysis of time to flare also supported that difference.

DR. CAPLAN: Were these placebo-controlled randomizations? Were the patients blind to that randomization?

DR. ROONEY: Yes. These are the patients who had received 4 milligrams in an originator study, done well enough to finish that originator study without needing to be rescued, and then they went into the long-term extension.

If they achieved sustained low disease activity of remission in the long-term extension, they then got to participate in that experiment. It just happened behind the scenes based on their disease activity.

DR. CAPLAN: Yes. My question is whether they actually had a placebo. In other words, I understand that they were randomized. My question is, did the patients who went from 4 milligrams to 2 milligrams receive a placebo that looked identical to the 4-milligram patients that remained on the 4-milligram?
DR. ROONEY: Thanks. Now I understand.

Yes. From an operational perspective, in the long-term extension, all the patients got 2 tablets from the beginning so that, when this happened, they couldn't possibly know whether their dose was being changed.

DR. CAPLAN: Thank you.

DR. SCHER: Very well then. We have five minutes for further clarifications.

DR. McGILL: We thank you very much. There are three topics we want to get back to, what we heard. I think we have some answers that the committee has asked for. Dr. Rooney, can you start off with some of the efficacy analysis? There was concern we were only showing one of them and we want to make certain you have the information you want.

DR. ROONEY: Yes. Terence Rooney, Lilly, thank you. We closed on the theme of the importance of understanding the difference between the doses for more refractory patients and also on the theme of, it's difficult to follow whether or
not we were presenting a sufficient breadth of outcome measures and time points for that topic.

Also, how do you pick the right outcome measures and time points for the topic of heterogeneity testing around this idea that more or less refractory patients might have different needs for the two doses?

So to the first question, here are the pre-specified results from study JADW. This is in the biologic refractory patients and this is a slide that was in the core presentation.

So we picked the continuous composite disease activity scores to illustrate differences between the doses because that's consistent with FDA guidance. Continuous measures are a bit more sensitive for detecting differences between the doses.

We looked across the full range of the time course and saw statistically significant differences favoring the higher dose in a retrospective analysis, of course. The prospective statistical testing between individual doses and
studies is not the norm in individual trials.

So here are two of the four available composite disease activity scores. There are two others that are commonly used. That's CDAI and DAS28 ESR. The same pattern was seen for both with the same pattern of statistical significance between the two doses over time.

Maybe a more agnostic way to look at the breadth of measures reflecting the disease control of these patients is to look at the individual core measures of the ACR core set. So here are those results just for your consideration.

So you'll see the first four measures of the core set on the left, the joint counts, swollen joint count, and tender joint count. You can see the pattern of differences between the three treatment groups and you can see indicated where there was and wasn't statistical significance between the active therapy and placebo.

On the right-hand side, you have the ask-the-doctor and ask-the-patient. And again, you can observe the pattern there. And if I move to the
next slide, you'll see the remaining measures of
the ACR core set, patient pain at the top left,
physical function at the bottom right. It was the
one measure that didn't discriminate particularly
well between the two doses. It's often a measure
that doesn't do that in clinical trials.

Then finally, to round out the suite of
measures, you can see the acute phase markers and
you can see for yourself the pattern of dose
response there. I think the other observation I'd
highlight here is that the responses were seen
eyearly and the differences between treatment groups
were well sustained over time. We didn't observe
the lines converging between weeks 12 and 24.

The last topic I'll just hit on then is the
topic of heterogeneity testing. So here's the
slide from the core presentation again from study
JADX, where we examined the concept of whether the
patients who'd failed only a single DMARD versus
those who had failed multiple DMARDs had a
different dose response.

Again, we thought it was important to look
at the full time course, not just, say, week 12, for example. This might be illustrated on the left-hand side. You can see the lines pop one way or the other in different directions at different time points.

So what we did with respect to heterogeneity testing was, we actually looked at every time point in the time course throughout the whole trial. And what we saw was at the individual time points. Of the 6 time points between weeks 12 and 24, at 5 of those time points, we saw a statistically significant interaction and stepping back again and being even more agnostic to which time point you might pick, we looked at the area under the curve of the full time course, the full burden of disease activity over time, and tested it, and looked for the same interaction there for two measures, this SDAI measure and the other composite disease activity score, DAS28.

I have a forest plot up here for you just for your consideration. We found that, for both measures, there was a statistically significant
interaction whereby patients who had failed a single DMARD had comparable benefit for the two doses and those who had failed multiple DMARDs had an enhanced advantage of the 4-milligram dose.

Then I'll just remind you from our presentation that our exposure response modeling supported this idea, patients who had failed more previous therapies had a higher need for the higher dose. So I hope those observations might be useful for you in your deliberations. Thank you.

DR. McGILL: Dr. Krishnan? Sorry.

DR. SCHER: Dr. Jonas, you have a follow-up comment or question?

DR. JONAS: Yes. I just had a follow-up question. Can you put up that slide that you've shown on the JADW study with the core measures? And I just want to make sure I'm understanding this correctly.

DR. ROONEY: So here are the first four.

DR. JONAS: Exactly. So what we're seeing here are the core measures and the statistical significance we're looking at is versus placebo.
The question I have is, what is the statistical

DR. ROONEY: For the core measures, these are the pre-specified results of the trial. So there was no statistical comparison between the doses. You can see the shape of the dose response yourself.

DR. JONAS: Right.

DR. ROONEY: The couple of observations I might have would be, for instance, for swollen and tender joints, 2 milligrams wasn't statistically significantly different from placebo on a consistent basis.

If I go to the remainder of the core measures -- excuse me, wrong slide; could we get the remaining core measures; perfect, thank you -- we had the same observation, for instance, for the acute phase marker ESR.

The statistical testing between doses that we conducted for each of the four composite disease activity scores, Dr. Jonas; mDAS, DAS, CDAI, and SDAI; showed that, at every single time point, a statistically significant advantage for the 4-
milligram dose, we conducted that in response to our observation that FDA was conducting between dose significance testing and in their briefing book.

We did have one set of pre-specified statistical tests between doses and that was the dose taper experiment that we discussed just a few minutes ago. That was explicitly designed to compare between the two doses and we reviewed those results just a moment ago.

DR. SCHER: Thank you very much. The last question will be coming from Dr. Russell.

DR. RUSSELL: Jon Russell, San Antonio. I wanted to address the issue of thrombocytosis and D venous thrombosis and pulmonary embolism again. Most of the rheumatologists in this room will recall what happened with Vioxx. Vioxx was a designer drug developed specifically to fit in the receptor and it did that beautifully. But then it turned on its maker and caused some other problems because it was so effective at binding to a receptor. It looks to me
like the submitted drug binds very effectively to JAK2.

If Dr. Whittaker's proposal is correct, then it may be responsible for the thrombocytosis. That increases the risk of clotting in veins and arteries. But on the other hand, we've known since about 1970, the early '70s, that thrombocytosis is a characteristic of active rheumatoid arthritis.

So the thrombocytosis that occurs in patients being treated with baricitinib, you could imagine might be added on top of that or in addition to the rheumatoid arthritis thrombocytosis.

The thrombocytosis of rheumatoid arthritis is blamed on the severity of the inflammation and correlated with it. And I'm sure that, in these studies, the investigators have attempted to enroll very active disease patients.

So they might have increased or enhanced the number of rheumatoid arthritis patients with thrombocytosis. It would be interesting to see what would happen if, rather than just correlate,
looking for a correlate of deep venous thrombosis with thrombocytosis, if it were digitalized; that is, they either had thrombocytosis or they didn't. Would either of those groups be selective for thrombophlebitis?

Would that help us understand what we're dealing with? And I'm afraid that we're having a combination of things in which JAK2 is contributing to something that is already there. The question is how they facilitate each other and whether that is the cause of the deep venous thrombosis.

I think the patients who have advocated for approval of this agent would not be doing so if a family member had had a pulmonary embolism and died from a medication that had a quirk. And so I think we need to be cognizant of that as we evaluate, make decisions about this drug.

DR. SCHER: Thank you, Dr. Russell. We will have plenty of time for discussions around that area. I believe you have one minute. That is 60 seconds.

DR. McGILL: Dr. Krishnan?
DR. KRISHNAN:  Gary Krishnan, discovery research, Eli Lilly. Thank you for the opportunity. I want to congratulate the FDA for investing a lot of time on the mechanism of action, which is often ignored.

What I've shown here is some supporting evidence and supporting data to offer as added information that is evidence-based from our JADV trials. These are the trials in which 4 milligrams of baricitinib was provided to the patient times 0. I want to draw your attention to 0 at the top panel, which was shared prior by Dr. Melissa Veenhuizen.

The bottom panel has not been reviewed or shared with the FDA, but it's exploratory and helps add information to this discussion. We can see that, in these patients, if you draw your eyes to 0 on the top panel, as baricitinib is given, there's an increase in platelet count at two weeks, which is as shown before, which then comes back down to about baseline or near about baseline.

What is important and perhaps most striking
is the concomitant decrease in mean platelet volume that is measured at the exact same time when these platelets were being recognized for platelet count.

What this tells us is that there is no new platelet synthesis occurring at the time when the vast majority of the platelets at the two-week time point represent older, mature platelets that are poorly being cleared from the liver.

This graph also tells us that at no time do we see new thrombocytosis or new formation of platelets, as those are typically associated with larger sialylated platelet volumes. Unfortunately, in order to protect our patients, we care more about the VTE and this is the correlation between all the platelet endpoints.

I want to draw your eyes to the 0 at the left panel and, as you climb up the Y axis, every time the blue dot stops is when our patient had a VTE. Those are the 42 patients who experienced a VTE.

On the left panel is the baseline platelet count as correctly pointed out by the distinguished
panel member, that these patients have a varied amount of baseline platelet counts. There is no accumulation risk at the start of treatment. The middle is the change in platelet count prior to their VTE event.

The last panel or the last graph is the difference between the baseline to this inflection. This is a classic depiction of a scatter plot. And it informs us that no platelet endpoint correlates or helps us inform the risks that our patients felt.

DR. SCHER: Thank you.

DR. KRISHNAN: We do believe, however, that this is an important and potential risk.

DR. SCHER: I'm sorry.

DR. KRISHNAN: We will continue to monitor it. Thank you.

DR. SCHER: We're up to 240 seconds. In this era of alternative facts, we also seem to have alternative time. Very well. We'll move on.

Dr. Nikolov will now provide us with a charge to the committee.
Charge to the Committee – Nikolay Nikolov

DR. NIKOLOV: Thank you, Dr. Scher. Good afternoon, everyone. As we prepare for the committee discussion in voting this afternoon, I want to provide a brief reminder of the scientific issues, the regulatory framework, and the questions to be discussed and voted upon.

The data submitted by the applicant demonstrated the efficacy of baricitinib in rheumatoid arthritis at doses of 2 milligrams and 4 milligrams once daily for the key domains required for approval of signs and symptoms or clinical responses by ACR response and other measures of clinical response and for physical function assessed by HAQ-DI response.

In studies that included both doses of baricitinib, the data were not consistent in showing a meaningful benefit of the 4 milligrams over the 2-milligram dose. Based primarily on the integrated analysis discussed by Dr. Abugov, there is likely a difference between both doses.

That difference, if true, is likely small.
The data on structural progression, assessed by radiographic response, showed consistent efficacy of baricitinib, 4-milligram once daily dose.

Only one study evaluated the impact of baricitinib, 2 milligrams, on the radiographic progression, and the data from that single study were not as robust for the 2-milligram dose.

The applicant has proposed two doses of baricitinib for marketing. Whether there is additional benefit of the 4-milligram dose compared to the 2-milligram dose of baricitinib is a topic of discussion and voting at today's meeting.

This is important because of the dose-related safety issues noted in the clinical program as discussed in the presentations today. The FDA reviews identified the safety profile of baricitinib consistent with a potent immunosuppressant with major safety risks of serious and some fatal infections, including opportunistic infections and tuberculosis, malignancy, laboratory abnormalities, increase in platelet counts, decrease in neutrophil counts, and
increase in lipid parameters, liver function tests, among others.

Many of these adverse reactions appeared to be dose dependent. Additionally, arterial and venous thrombosis were observed in association with baricitinib treatment. While many of the adverse reactions are typical for immunosuppressive therapy used for rheumatoid arthritis patients, the dose-dependent platelet elevations and reports of thrombotic events are noteworthy.

FDA considered a plausible mechanism related to JAK inhibition and platelet elevation as discussed by Dr. Whittaker.

One of the challenges of the baricitinib clinical program was the assessment of safety. As with other RA programs, there was a limited placebo-controlled period and patients could escape or crossover to the higher baricitinib dose.

Often, when most of the safety data are from baricitinib treatment groups and there are limited control data, interpretation of imbalances in adverse reactions between treatment groups is
problematic and challenging.

In addition, the fact that baricitinib 2-milligram dose was only included in 2 of the 3 phase 3 clinical studies complicated assessment of the safety of the baricitinib 2-milligram dose.

To address some of these limitations, several strategies to combine the safety data were used. These strategies, however, cannot overcome the limited placebo-controlled data and the limited safety database with the baricitinib 2-milligram dose.

In summary, while the efficacy data are consistent with the treatment effect of baricitinib versus placebo, the results from the individual studies were not consistent with a meaningful benefit of the higher versus the lower dose.

Further, while the data supporting the radiographic response are robust for baricitinib 4-milligram once-daily dose. There is some uncertainty about this effect for the 2-milligram dose, which was studied in only 1 phase 3 study as an exploratory endpoint.
We note that the baricitinib program followed the historical approach to dose selection, specifically pushing the dose high enough to demonstrate a marketing advantage versus standard of care; in this case adalimumab and methotrexate.

This approach may result in counterbalancing safety. While we recognize the numerical differences in efficacy between the 2 milligrams and the 4-milligram doses, which were most obvious in the biologics DMARDs incomplete responders, which is not the sought indication, the question we would like the committee to focus on is whether the numerical differences in efficacy justify the additional risk in the indication sought for licensure, especially if that risk has not been well quantified and characterized, which can be challenging at the very least, as you heard today, even in the controlled setting of a clinical program.

The majority of the safety data are with the higher dose of baricitinib, 4 milligrams. And the identified safety issues raised concern regarding
that dose.

The limited safety database with the lower dose complicated the benefit-risk assessment of the 2-milligram dose of baricitinib.

The next few slides are included for reference of the regulatory framework used by the agency in the review and regulatory decision making for drugs. An applicant is expected to provide substantial evidence of efficacy consisting of adequately and well-controlled investigations that the drug product will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

With respect to safety, an application can be refused to be approved in one of several circumstances, as listed in this slide. These include information that the drug is unsafe or that there is insufficient information about the drug to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

With this background, the first question for
the committee to discuss is the efficacy data of baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

We ask that you include a discussion of the 2-milligram and 4-milligram doses of baricitinib and whether available data support a benefit of one over the other.

Then the committee will be asked to vote whether the data provide substantial evidence of the efficacy of baricitinib for the treatment of adult patients with moderate to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate for each of the proposed doses, 2 milligrams and 4 milligrams once daily.

If you voted no, we ask that you discuss what additional data, if any, will be needed. If you voted yes, you can also provide comments.

The next discussion point relates to the safety of baricitinib in the proposed indication,
where we would like to seek the committee's input on the adequacy of the safety database for the 2-milligram dose of baricitinib, the adverse events of special interest, and whether the safety data are more favorable for one dose versus the other.

Then the committee will be asked to vote on whether the safety data are adequate to support approval of baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate for each of the proposed doses, 2 and 4 milligrams once daily separately.

If you voted no, we ask that you discuss what additional data, if any, will be needed. If you voted yes, you can also provide comments.

The last two voting questions are on whether the overall risk-benefit profile is adequate to support approval of baricitinib for the proposed indication for each of the proposed doses, 2 milligrams and 4 milligrams, separately.

If you voted no, again, we ask that you
discuss what additional data if any would be needed. And if you voted yes, we would welcome any comments. Thank you.

Questions to the Committee and Discussion

DR. SCHER: Thank you, Dr. Nikolov. We will now proceed with the questions to the committee and panel discussions, I would like to remind the public that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

As a clarification, we will be using an electronic voting system. Once we begin the vote, the buttons will begin flashing and will continue to flash even after you have entered your vote. So please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the
screen. And then we will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did. We will continue in this same manner until all questions have been answered or discussed.

So the first question, which is a discussion point -- and I will read as is -- is to discuss the efficacy data for the treatment of adult patients with moderately to severe active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

It should include a discussion of the 2 milligrams and 4-milligram doses of baricitinib and whether available data support a benefit of one dose over the other. Dr. Brittain?

DR. BRITTAINE: So in terms of the first part of this question, I think it's pretty easy that we have good evidence of efficacy. The second part is harder, the 2 versus 4. I mean, I think, in some ways, there's some aspects of the data that do
point to a difference, for example especially in
the sicker patients in that the JADW study, which
is only of the sicker patients, were seeing
significant differences, if I'm understanding
correctly on some of the endpoints, but perhaps not
all the endpoints at various times.

   Similarly, in the other study, other head-
to-head study, the JADX when you look in the sicker
subgroup, there's some suggestion of some
difference at least with the SDAI variable, I
believe.

   Whether this is true across the board and
all the variables is not quite -- I'm a little
confused about whether that's true. And what may
be the most important thing -- and I can't really
answer -- is whether this difference is meaningful,
clinically meaningful.

   But there does seem to be some evidence
that's not totally clear-cut, but some evidence
that the sicker patients do better with 4.

   DR. SCHER:  Dr. Oliver?

   DR. OLIVER:  Alyce Oliver. I have more of a
question, a clarifying point back to the FDA. I agree with Dr. Jonas and Dr. Brittain. The question is about this subgroup that is more refractory to treatment. And is this a clinically meaningful difference in this subset of patients?

Can you again kind of summarize the JADW in terms of your analysis and why you don't think it's significant or why it comes together at the 2 milligrams and 4 milligrams at 12 weeks.

DR. NIKOLOV: This is Nikolay Nikolov. Just to clarify, you're asking whether we considered the results from study JADW, not meaningfully different between the two doses?

DR. OLIVER: Right.

DR. NIKOLOV: I'll ask my statistical colleagues and then I'll add to that. So maybe while they get ready, I don't think we argue with the data. I don't think we want to convey the message that's in that setting, that the 4 milligrams is not better than the 2 milligrams.

However, the sought indication is a much broader indication which includes essentially
anyone that has failed methotrexate. And

certainly, in that patient population, we have
major concerns about any meaningful differences
between the two doses.

DR. ABUGOV: I'll just add -- this is Robert
Abugov -- a couple of quick notes. I brought my
review down from my office during lunch. For study
JADW, at week 12, the odds ratio between the
baricitinib 4-milligram and the 2-milligram dose
for ACR20 was 1.3. The difference was not
statistically significant.

If you go all the way to ACR70, the ratio
was 0.6, which goes in a direction of advantage for
baricitinib 2 milligrams. And again, this is why
we have doubts about whether in a specific
subpopulation the 4-milligram dose is superior to 2
milligrams.

Again, in the general population, we do see
evidence of a difference which does not seem to
reach minimal clinically important differences.

But we do believe in the general population
that the difference is there.
DR. BRITTAINE: Actually, I just wanted to ask you a follow-up question. I just want to make sure I understood what you just said there. Did you say, for JADW, which is a study that's only in the refractory patients, right --

DR. ABUGOV: Yes.

DR. BRITTAINE: -- that even in that study, when you use the ACR70, that the odds ratio went in the opposite direction. Is that what you said?

DR. ABUGOV: Yes. It was 0.9, but again, the difference was not statistically significant. The p value was 0.6.

DR. BRITTAINE: But very few patients reached that. Is that right? Is that a very small proportion?

DR. ABUGOV: It's a very small proportion, yes.

DR. BRITTAINE: Thank you.

DR. SCHER: Dr. Caplan?

DR. CAPLAN: Can we just have clarification, Dr. Nikolov, maybe, regarding the initial submission for the indication under the initial
submission and the change in the indication now and what specifically is different and what your concerns are about that?

   DR. NIKOLOV: So the proposed indication in the original submission was very broad, essentially treatment of adult patients with active rheumatoid arthritis, which was all encompassing. Now, with the resubmission, the applicant recognized the risk-benefit and the safety concerns that we had and proposed a more narrow indication, which requires some pre-treatment or failure to some background standard of care like methotrexate.

   So in a way, that's a more narrow indication compared to the original proposal.

   DR. CAPLAN: So the original propose was not in incomplete responders. It was just in adult moderate to severe RA?

   DR. NIKOLOV: Correct.

   DR. SCHER: Ms. Aronson?

   DR. ARONSON: Just clarification, too, about the 2 milligrams; I wrote down my notes and I'm not sure which study this is, but the review by the FDA
of 2 milligrams said that only 200 patients were available for the one-year study and that the FDA requires 1,000 patients for one year for review.

Is that correct

DR. NIKOLOV: So there is a recognition over the years that most of the products used to treat rheumatoid arthritis are immunosuppressants. And for many of these, there are latent toxicities in particular with malignancies in some later infections and to capture these usually requires longer-term and larger sample size.

Our thinking has evolved over the years and the current thinking is that the safety database, about 1,000 to 1,500 patients exposed for one year on the proposed marketed dose would be optimal to pick up these differences. And not only that, but ideally this should be controlled data so we can have meaningful comparisons to something either standard of care or something else to draw some conclusions about the numbers that we see at the end.

That's one of the challenges that we had
with this application, that for the higher dose, which is again the intended dose to be marketed, the numbers are fairly large and patients are followed for a long period of time. A lot of it is uncontrolled, but at least the numbers are there.

For the lower dose, they were only included in a couple of studies and the sample size is fairly small, even if they are followed for a longer period of time. So that's where we have the uncertainty about the point estimates or confidence intervals around these events in the lower dose of baricitinib.

DR. SCHER: Do you think you can walk us through the process of how you know the doses are being chosen? Clearly, the sponsor goes for the indication that they think will be approved based on efficacy. I'm sure I may be wrong that there's a discussion to be had for lower doses. And the question I may have and probably the rest of the panel is, why stop at those 2-milligram indications when this is a possibility for when it comes to approval to the drugs, I mean, having had the
experience of tofacitinib, where that clearly was what happened in the end, going for the lower dose?

DR. NIKOLOV: Thanks for the question. I think this is a very important question to be addressed in any drug development, but in the field of rheumatoid arthritis, because there are so many drugs approved and we deal with toxic drugs, I think this is even more imperative that upfront investment in good dose selection is critical.

We certainly acknowledge that the applicant has conducted dose-ranging studies. And at the time when they decided to move to the phase 3 development program, they had sufficient information to justify going with these two doses. They had additional information from another phase 2 study which showed the inconsistency between the 2 doses in efficacy, which raised additional questions of whether these were the optimal doses.

I think it's certainly good maybe for the committee also to weigh in and discuss whether additional benefit-risk can be assessed in lower doses. And I think that's an open point for
discussion. That was also one of the considerations in the complete response letter with this application.

DR. SCHER: Thank you. Dr. Kim?

DR. KIM: So I have a question to either FDA or the applicant about the drugs, the 2-milligram dose effect on radiographic response. I know, in the FDA presentation, there was a table that showed what the applicant did with using linear extrapolation versus using just observed data.

I think, in multiple places of today's presentation, it was emphasized that 2-milligram effect on radiographic progression wasn't very robust. So I just wanted to kind of have an idea, with regard to other approved DMARDs, what would be the expected reasonable effect on this?

DR. NIKOLOV: So this is Nikolay Nikolov again. I will try to take this. Just to remind everyone, radiographic endpoints are a desirable outcome and desirable clinical assessment for both clinicians, prescribers, and patients.

However, FDA has not considered this to be a
required endpoint for the approval of a product. We base approvals primarily on the clinical response and physical function. Your question certainly raises a lot of interesting questions about the interpretability of the radiographic data.

I think, at this point, we can only reference historical experience where most of the products approved are approved based on linear extrapolation of missing data. And it's a bit more complex to discuss the appropriate statistical analysis.

But there is no ideal way to analyze radiographic data short of head-to-head active comparator data without loss of data, without missing data. So unfortunately, placebo-controlled studies are of short duration and, within that time frame, it's very difficult to demonstrate differences in radiographic endpoints, which complicates the analysis where patients transition or escape. Their data is more or less lost.

I think we have spelled out in the RA
guidance that, currently, analyzing radiographic data is challenging. And we see it even more problematic in going on in the future, where placebo-controlled studies will be of much shorter duration.

DR. WANG: Ms. Horonjeff?

DR. HORONJEFF: Hi, Jen Horonjeff. This is kind of my thought process, thinking about it from the patient perspective of -- and I know we're just talking about efficacy, but I do appreciate that they were measuring pain, and swollen joint count, and things that are important to patients.

I just want to have those options for patients to be able to get those higher doses if needed. So while there may be different things to weigh out, I still lean towards making sure that the patients have the options, especially if they've failed other biologic DMARDs.

I know that that's not the way that this indication is saying. But knowing in the real world how we cycle through these medications and as some of our speakers here today said, I just want
to make sure that patients have the options they need if they're failing these other medications and they need the extra boost.

DR. SCHER: Thank you. Dr. Miller? Where is Dr. Miller?

DR. MILLER: Hi, Don Miller. I think one other thing that's not been talked about very much is the speed of response. The FDA analyses didn't look at that, but as a clinician, I think that, when patients can have faster response, that is meaningful.

So although the overall difference between doses may be fairly small, the higher initial dose I think, has some real benefits.

DR. SCHER: Appreciate it. Dr. Oliver, let me just remind you that the main topic of discussion for this particular aspect is to get your insights into whether either of those should be approved on the basis of efficacy. And I don't think we're focusing on the latter, which is the step-down approach.

While I appreciate the comment, I think the
question that we are being posed with is whether or not the efficacy data on either dose or both are statistically relevant.

DR. OLIVER: Alyce Oliver. It is not a question about efficacy, but it goes down to the stepdown. I had a question for Dr. Nikolov. In your initial briefing, you discussed that it's not usual to have in the package insert to have a stepdown. Does that mean it's never happened or it should not happen?

DR. NIKOLOV: So this is Nikolay Nikolov. I think it was more of a general comment, that we defer this to the discretion of the prescribers, to give them the flexibility to decide how and when.

I can say that we would encourage clinical trial designs of that nature to inform prescribers. Whether that would end up being in the label is a separate question and, again, we think more in the context of allowing the prescribers to make these decisions without us specifically proscribing or spelling it out in the labeling.

Just one caveat that, unless we have safety
concerns; for example that patients may need to
dose taper it down because of safety, for example,
abnormalities, we have done this.

Sarilumab was approved with that dosing recommendation, that patients can go to the lower
dose if they have laboratory abnormalities.

DR. SCHER: Other questions or discussion points, Dr. Kim?

DR. KIM: This is Seoyoung Kim. So I'm thinking, mainly focusing on the 2 milligrams
effect on patients who are inadequately responsive
to biologics, so that's a slide related to the JADW trial.

So according to the applicant's presentation, there was a light green column for
the 2 milligram versus placebo versus when they
compared 4 milligram with the placebo, it was dark green, which they said it was statistically
significant with the multiplicity control.

So I was just wondering, I guess by
definition, it wasn't statistically significant
when you control for multiplicity? But I just
wanted to have a little bit more detail about the strategy there.

    DR. SCHER: Yes, please.

    DR. McGILL: Thank you. Dr. Beattie, can you please answer that? Thank you so much.

    DR. BEATTIE: Scott Beattie. Yes. So let me just give you a frame for that study. Because it was in the most refractory patients, what we did is, we evaluated all of the objectives for 4 milligrams first.

    It just so happened that, because one of them was not significant at week 12, although it was at all the later time points, we were just unable to evaluate those claims for 2.

    However, what I wanted to just show you is just based on the totality of the evidence from the two studies. What we saw was a highly statistically significant result in the other study, JADX. These are the same endpoints across the trials.

    In fact, it was significant to the level less than .001, which in some sense could stand as
a trial in its own. And then we saw replication
in the other study with similar estimates,
confidence intervals, and p values. So I believe
that's why we, the sponsor, and FDA concluded that
both doses actually are effective.

DR. SCHER: Does the FDA have any further
comment in that regard?

DR. NIKOLOV: I don't think we have anything
more, but we'll be happy to expand if needed.

DR. SCHER: So I guess the fundamental
question here is whether or not there is any
meaningful difference, either statistical or
clinical, between both doses. And that's the
question we're charged with.

Based on the data, if I may summarize what
we've been hearing so far, he said, depending on
the way we interpret the dataset. It's true that
baricitinib at 4 milligrams has a small
superiority, statistically meaningful efficacy
compared to the 2 milligrams, where there's no
difference whatsoever.

Does anybody have a different interpretation
so far of what the data between these two doses seem to be? Dr. Caplan?

DR. CAPLAN: Liron Caplan from the Rocky Mountain Regional V.A. I think what is unique about the data that have been presented so far is the withdrawal study. And I understand that we're not here to recommend whether or not that gets included.

So apart from that, I think it is an efficacy outpoint. It seems, at least from the limited data that we have available to us, that it was done in a rigorous manner with double blind placebo, and that there was a statistical effect that was physical across all the outcomes.

I think that that's what we do as physicians. Sometimes, we'll reduce the dose or make some change to see the effect and the patient will say, "Yeah, that's worse," and then it's an N of 1 study. But I think that's a unique and, in this case, compelling piece of evidence for me.

I think also the way that you phrased it was accurate, depending on how you look at it. You see
clear dose response across all these individual outcomes. The ESR looks differently, again not an important clinical outcome in and of itself, but it alludes to the fact that there are probably individual patients, some of whom are probably in this room who will respond to 4 and not to 2.

As a group, we can say that borders on marginal clinical benefit, but for individual patients, I personally feel compelled.

DR. SCHER: Thank you. Sean Curtis?

DR. CURTIS: Yes, hi, Sean Curtis. Just listening again as the industry rep, I just wanted to understand clinically why the debate and the focus on ways to assess and interpret the meaningfulness of the numeric difference we're seeing, but if I could just confirm with the FDA from a strict statutory perspective, showing statistical significance between doses is not a requirement for approval. Correct?

DR. NIKOLOV: Depends on the context, but in this context, yes. So the relevant comparison is to placebo, to demonstrate substantial evidence of
efficacy versus placebo.

DR. SCHER: Dr. Katz?

DR. KATZ: James Katz. So if we assume that
the 4-milligram dose does indeed reduce
radiological progression, we don't seem to have
data to make us comfortable that the same can be
ture of 2 milligrams and the danger is in reducing
the dose, maintaining clinical control, but not
maintaining radiological control and practitioners
being misled, so to speak, by that dose reduction
in the same way that we know of methotrexate making
people feel better, but not necessarily reducing
radiological progression, the disconnect between
clinical and x-ray.

DR. SCHER: Thank you, but just to
reiterate, it is not part of the FDA approval
process. It's strictly based on clinical efficacy,
with or without radiographic progression data.

DR. NIKOLOV: That's correct. Again,
recognizing that the radiographic outcomes are
relevant, again, that would not be a requirement
for demonstrating substantial evidence of efficacy.
DR. SCHER: Any words of wisdom from our statisticians?

DR. BRITTAIN: I'm not sure what to say because --

DR. NIKOLOV: Thank you, Dr. Brittain.

DR. BRITTAIN: Yes. I see it as unclear at this point. I don't think there's any way to definitively know whether 4 is better than 2. I would say, if I had to guess, my best guess is at a little advantage of 4 to 2 and perhaps most with the patients who are refractory.

I was interested in terms of the comment about the study that starts with 4 and then goes to 4 and 2. A, I'm not really sure which endpoints they looked at to say that there was a difference. I can't remember if it was pre-specified and they looked at the one that they were planning to look at. That, I'm not sure about.

It could potentially make a difference when you're starting with, if I'm understanding the design of that study, the people who have done well with 4, and then going down to 2 or 4 might be
different than starting with a group that's doing well with 2. I guess, if you're doing well with 2, what would happen if they randomized them to 2 and 4?

So it might have been a different answer.

DR. SCHER: Any further questions or comments before I summarize? More of the confusion than the certainties. Diane, you have a comment?

DR. ARONSON: I want clarification. I wrote that only 300 patients randomized down to 2 milligrams. Is that true?

DR. NIKOLOV: Maybe the applicant can clarify.

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thank you. Terence Rooney, Lilly. I'll just draw your attention to the slide on the screen here. So here are the numbers who were randomized at the time of the data cut that we used for this resubmission in April of last year in this experiment.

This is confined to the patients who would be pertinent to the proposed indication; in other
words, they had failed at least one DMARD, predominantly including methotrexate.

So you can see the number here is 435 versus 439. If I could bring up the efficacy slide, then, that we showed during the core presentation, I think what you're getting at is -- slide up here -- that the numbers at the bottom row aren't identical to that.

By the time you get out to week 48, it's 376 versus 374. So this is not the same pool of patients dropping out over time. This is the week 12 results are in the people who had been re-randomized at least 12 weeks before the cut. And that's the same pool as the week 24, as it happens. Then the later folks, week 36 and 48, are the pool of patients who have been re-randomized at least 36 weeks before the cut, so that each comparison is randomized. So I hope that clarifies.

DR. SCHER: Dr. Brittain?

DR. BRITTAINE: So I guess I'm wondering why you weren't looking at the ACR for that time point,
since that was the primary endpoint of the parent.

DR. ROONEY: Thanks. Again, Terence Rooney, Lilly. We conducted this experiment to match guidelines from ACR and European analog, European League Against Rheumatism, which for a number of years now have advocated this treatment strategy, that if patients do well on a given therapy, consider tapering the dose.

Don't stop altogether because people tend to flare and not do well, but consider tapering the dose. So we designed this experiment to inform the potential use of baricitinib according to those guidelines and this is the first time, to my knowledge, that such a thing is being done at the time of the registration program.

The reason we didn't use ACR20 for instance, which is the typical primary versus placebo, was twofold. Recall the guideline is that, when patients have achieved sustained disease control, consider tapering.

ACR response doesn't allow you to determine whether somebody has achieved sustained disease
control because you can't use it to say is somebody in low disease activity or remission. So we have to use one of the different composite measures.

Then the final question is, well, why did we pick CDAI, and not SDAI or DAS, et cetera? Very simple operational reason. You can do CDAI on the spot in the clinic. You don't have to wait for the result of a blood test to come back. And so when the doctors see the patient on a Monday morning in the clinic as part of the study and plug in their joint counts and disease activity clinical scores, the system receives it immediately and can randomize them on the spot.

DR. BRITTAIN: Again, that was your pre-specified endpoint?

DR. ROONEY: It's all pre-specified.

DR. BRITTAIN: Can we see that slide again? I just want to make sure.

DR. ROONEY: Yes, certainly. And so because that was the measure that allowed you to be included in the study, it was also the pre-specified principle outcome measure, yes.
Now, we did support this set of observations as I mentioned briefly earlier, with looking at the change from the time of randomization to each of these landmarks in each of the composite disease activity scores, not just CDAI, and all of their components.

It showed the same thing, a statistically significant advantage of 4 over 2. And we also supported it with another pre-specified analysis that's time to last disease control, which showed the same thing.

DR. NIKOLOV: Dr. Scher, just one point of clarification?

DR. SCHER: Dr. Nikolov, please?

DR. NIKOLOV: Yes. I just wanted to give a bit more of a context for the interpretation of the data from this study. And again, we're not arguing with the data. We certainly encourage this trial design to inform what should happen once the patient is responding to a drug.

But that answers a different question than what we're asking, which is, which should be the
starting dose, keeping in mind that these are patients who already responded to the 4-milligram dose and some of these are patients who upgraded from the 2-milligram dose in the previous studies.

So the study again is informative in a different context, not specifically to the question that we are asking.

DR. SCHER: Thanks for the clarification.

Dr. Bilker?

DR. BILKER: Yes. I wanted to ask the sponsor if you have that same taper data analysis in the subset of patients who have failed more than 2 or more DMARDs. I'm wondering if those are the group that you're not able to taper.

DR. McGILL: Dr. Rooney?

DR. ROONEY: Thanks, yes. Terence Rooney, Lilly. So that would be the group of patients for whom 4 milligrams would be indicated in our currently proposed recommended dosing paradigm.

So I'll bring that up on the screen now and you'll see, just to orient you, on the left-hand side the overall results, so on the core
presentation, and then on the right-hand side the analog in, that subgroup of patients.

We found the same thing, is the short answer. So here are the results on the screen here. I'll let your eye wander across it. And we saw a similar pattern.

DR. BILKER: That indicated you are able to taper some of those patients.

DR. ROONEY: Yes, indeed. This tells us, I think, two things. You need to hold two seemingly contrary ideas in your head when looking at these data. On the one hand, 4 milligrams is superior to 2 milligrams in that maintenance context, as evidenced by this experiment.

On the other hand, for a large majority of patients who tapered, they continue to maintain control at the height of the gold bars, suggesting that it's a reasonable treatment strategy.

A really important part of that determination is whether or not people who do lose control after tapering to 2 milligrams can recapture after return to 4. Earlier studies in
this area had suggested that, that might be a problem.

The patients who tapered and then re-escalated back to 4 were able to recapture.

DR. SCHER: Very well. Then I will go ahead. And Dr. Brittain has the last word.

DR. BRITTAIN: I'm sorry; one more question, and this is really my not understanding. And maybe you've already discussed this and I didn't absorb it. Is there any reason why you can't go the other way, which is to say we start with 2 and everybody see how they do? And then if they need to go up, we go up. Is that operationally possible to do it that way?

DR. NIKOLOV: So this is Nikolay Nikolov. I think we would like to have information to inform the labeling and the prescribers on what circumstances that would happen short of saying as clinically indicated, for example.

DR. SCHER: There is a recent example, maybe more than one, but secukinumab has that on the label, where you can start at a dose and then
double the dose. Were there trials conducted prior to that indication for that particular label?

DR. NIKOLOV: Yes. I don't think I can comment on other applications at this time. But in general, if there is no safety concern, we would consider flexibility on dosing in general. When we have a safety concern, particularly one that's not well characterized and we think might be dose dependent, that's certainly a red flag for us, pausing and thinking about a scenario where we would allow dose escalation without any specific guidance.

DR. SCHER: Thank you very much. So I will summarize now if I can. I guess there are two main aspects of this discussion. One is that it seems to be an obvious consensus on the fact that both 2 milligrams and 4 milligrams are robust clinically and superior to placebo.

Where the discussion is occurring is whether or not bari at 4 milligrams is superior to 2 milligrams at all. There seems to be data that can be interpreted differently, depending on which
approach either the FDA or the sponsor go with.

Dr. Oliver suggested that perhaps the most relevant aspect of the discussion is in the refractory group and whether or not there's a clinically relevant difference between those that now use the 4 milligrams, those patient studies, versus those that are on the 2 milligrams or the stepdown.

The FDA appears not to be convinced of the way the data is interpreted. They do say -- and this is Dr. Abugov -- that at week 12, which I may remind you that that's the primary endpoint -- there seems to be either no statistical differences between the doses or small benefit comparing 4 versus 2.

In fact, when they do some further analysis, it seems to be that the 2-milligram dose may have an event superior outcome compared to the 4. That's a numerical game and does not appear to reflect reality. Dr. Caplan asked the question of whether or not anything has changed in terms of education.
The answer seems to be, yes, that in the resubmission, the indication has narrowed down to those individuals that now are methotrexate inadequate responders. And then the question was posed about how many patients do we need in randomized controlled clinical trials to really assess the efficacy and the safety.

We'll discuss safety later for one particular dose. In the case of 2 milligrams, the FDA is not necessarily convinced that we have enough exposure in this particular program.

Dr. Kim and Dr. Katz had voiced certain concerns about the fact that the radiographic data is either not interpretable or robust enough to decide in between 4 and 2 milligrams.

There was a healthy discussion specifically by Ms. Horonjeff about the idea that having a dose range is relevant in clinical care. And I guess that was the last part of the discussion.

Again, summarizing good evidence, robust for either versus placebo, no real consensus when it comes to understanding whether the 2-milligram data
is enough for us to understand whether or not there are differences between 4 milligrams and 2. Ms. Aronson?

DR. ARONSON: Sorry, one point of clarification --

DR. SCHER: Before I go into it, yes.

DR. ARONSON: -- on that; is the sponsor asking for approval of 4 milligrams? So what we're discussing about 2 milligrams is not necessarily relevant?

DR. SCHER: Dr. Nikolov?

DR. NIKOLOV: Yes. So the recommended dose or proposed recommended dose by the applicant is 2 milligrams for the indication which is on the slide. And then for the 4 milligrams, the applicant is proposing essentially a second indication or separate population, which is a population who had failed or had an inadequate response or intolerance to 2 or more DMARDs, which is a different group of patients than the principal indication.

DR. SCHER: So if there are no more
comments, we will read out the question, which will be question number 1, do the data provide substantial evidence of the efficacy of baricitinib, 2 milligrams once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

If your answer is no, please state which data is needed. Reminder that you should press the button on your microphone that corresponds to your vote. You will be approximately 20 seconds into the vote. So please press the button firmly after you have made your selection. The light may continue to flash.

If you are unsure of your vote or wish to change your vote, please press the corresponding button again after the vote is closed.

(Voting.)

DR. SCHER: Everybody's voted. So the vote is now complete. This looks like the Oscars ceremony now. And the winner is -- just so you
know, now that the vote is complete, we'll see the
results in a little bit. We will go around the
table and have everyone who voted state their name,
the way they voted, and if you want to, you can
state the reason for why you voted as you did so we
can record your vote.

That's number 3. So we will start with
Dr. Caplan.

DR. WANG: For the record, we have 14 yeses,
1 no, 0 abstain.

DR. SCHER: Dr. Caplan, your name, the way
you voted, and if you want to, explain why?

DR. CAPLAN: I'm still Dr. Caplan and still
from the Rocky Mountain Regional V.A. I voted in
favor. I just found the effects consistent across
multiple subgroup analyses and I did find it
compelling that there was a group of patients that
seemed to respond at the 2-milligram in the placebo
trials.

DR. SCHER: Thank you. Dr. Russell?

DR. RUSSELL: Russell. I voted no because,
if I were starting an active rheumatoid arthritis
patient on a medication right now, I would want to
be able to assure them that they would find
improvement in their x-ray. And I didn't hear
adequate data to support that.

Clinically, I think it's true that it would
be effective, clinically.

DR. SCHER: Thank you. Dr. Kim?

DR. KIM: Seoyoung Kim, I voted yes
because, based on the data presented today, I feel
pretty confident about the effect of bari 2
milligram over the control group they had. And
then I voted yes because the question was not
specifically asking whether 2 and 4 is different,
so that's a different question. If someone is
asking 2 versus placebo or control, I would say
yes.

DR. SCHER: Dr. Miller?

DR. MILLER: Don Miller. I voted yes. I
thought both of the placebo-controlled studies
showing the 2 milligrams were superior.

DR. BRITTAINE: Erica Brittaine. I voted yes.
The primary analysis in both studies was very
significant. And even in terms of radiographic
evidence being a little less than you'd want, since
it's not required and it at least was some evidence
with the linear interpolation method, I'm not that
concerned.

DR. ARONSON: Diane Aronson. I voted yes
for it showing superiority in the studies, in the
controlled studies for placebo.

DR. HORONJEFF: Dr. Horonjeff. I'm the
consumer representative. I also voted yes because
I do believe that the data suggested it is superior
over the placebo.

DR. JONAS: Beth Jonas. I voted yes.

DR. BOUDREAU: Denise Boudreau. And I voted
yes. I thought the evidence presented from both
JADX and JADW support that the two milligram is
superior over placebo for the main endpoint, but
also at the other endpoints.

DR. SCHER: Dr. Scher. I voted yes. I'm
not that concerned about the radiographic data.
Patients don't necessarily look forward to seeing a
not necessarily clinically relevant lack of
progression, of radiographic data, and therefore
the clinical data is robust.

DR. OLIVER: Alyce Oliver. I voted yes. I
agree the clinical data was robust. I do look
forward to seeing longer-term data, though.

DR. KATZ: James Katz. I voted yes.

DR. BILKER: Warren Bilker. I voted yes. I
thought the evidence of efficacy was strong.

DR. ORTEL: Tom Ortel. I voted yes on the
basis of the clinical data that I saw.

DR. IWATA: Soko Setoguchi. I voted yes,
same comment with others.

DR. SCHER: So this will be question number
2. Do the data provide substantial evidence of the
efficacy of baricitinib, 4 milligrams once daily
for the treatment of adult patients with moderately
to severe active rheumatoid arthritis who have had
an inadequate response or are intolerant to
methotrexate. If your vote is no, what data are
needed? You can vote now.

(Voting.)

DR. SCHER: Everyone has voted. So for the
DR. WANG: We have 15 yes, 0 no, 0 abstain.

DR. SCHER: We will go around the table again. Dr. Caplan?

DR. CAPLAN: Am I going to be first every time? That seems punitive. The data supported the results.

DR. SCHER: It wasn't punitive.

DR. RUSSELL: Russell. I voted yes because I think the data supported it both clinically and radiographically and because the response was quite rapid, within a month.

DR. KIM: Seoyoung Kim. I voted yes, no comment.

DR. MILLER: Don Miller. I also voted yes.

DR. BRITTAINE: Erica Brittain. I voted yes. It was an easy vote.

DR. ARONSON: Diane Aronson. I voted yes based on the data presented.

DR. HORONJEFF: Jen Horonjeff. I also voted yes.

DR. JONAS: Beth Jonas. I voted yes.
DR. BOUDREAU: Denise Boudreau. I voted yes.

DR. SCHER: Jose Scher. I voted yes.

DR. OLIVER: Alyce Oliver. I voted yes.

DR. KATZ: James Katz. I voted yes.


DR. ORTEL: Tom Ortel. I voted yes.

DR. IWATA: Soko Setoguchi Iwata. I voted yes.

DR. SCHER: So I guess we will continue with this discussion before we take a break. So we are charged with a discussion about the safety data for baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

We need to include a discussion of the following issues; A, adequacy of safety database for the 2-milligram dose of baricitinib; B, safety issues of interest and whether data suggest a dose response, including thromboembolic events, malignancy, serious infections, opportunistic
infections, herpes zoster, tuberculosis, and
abnormal laboratory parameters, specifically
elevations in platelet count, and then C, is the
overall safety profile of the 2-milligram dose and
the 4-milligram dose and whether the data are more
favorable for one dose versus the other?

Dr. Russell?

DR. RUSSELL: I guess I already commented
extensively about this issue, but there was a
statement in one of the pre-reviews that we had to
evaluate that indicated that rheumatologists are
used to looking for adverse events and monitoring
them and, therefore, it's reasonable to have their
patients undergo the risks that are listed in this
list of adverse events.

But rheumatologists do not typically look
for thromboembolic events. That's not been
traditionally among the list of things that they
watch for. I could see a rheumatologist watching
for thrombocytosis if that were meaningful, but
we're not even sure that that's true.

So my opinion is that the thromboembolic
events, since they do appear to be significantly higher than with placebo, that is a concern to patients. And the patient with thrombophlebitis will have symptoms. The patient who had a pulmonary embolism; it's already too late in many cases.

DR. SCHER: Thank you, Dr. Russell. Following up on that point, can I pick on you, Dr. Ortel, to give us a broad understanding of the DVTP clinical and prognostic scenario, how common this is, what are the implications, what happens after the first event?

DR. ORTEL: So there are a couple of issues that are going around here, one of them being the platelet count and whether or not the platelet count can serve as a surrogate marker for people who are at higher risk for thrombotic events.

That one, I think, is a little bit easier to address. And if I could go to slide 36, Dr. Nair's presentation, which had the platelet counts over time, just to put this in perspective, that's a delta. Okay? So if the average platelet count is
300,000, that means, with the high dose bari, it's going up to 350,000.

I have no data that tells me that that a delta within the normal range is significant or means anything. So you do have an interesting observation and an interesting effect, but I'm not quite sure what to do with that, if it means anything.

The issue is how many people does it make thrombocytic. And that's in the next slide, where they showed how many went above the upper end of the normal range, which is that 450.

So if you go across there, you see that patients on the highest dose, 61 of them actually went above that upper end of normal range. But at the same time, what I was told from both the sponsor and what I think I was also told by the FDA was that there was no relationship at all between clinical outcomes and any of these counts, either the delta or the absolute.

Now, the one thing that was missing in the VTE cases, that CO-83 slide, which would have been
helpful, would have been to have actually listed what was the platelet count at baseline, what was the platelet count at the time of the event, and what was the delta from the Lilly presentation at CO-83.

So you had the 6 events, but we don't have any relationship to anything. So I think that the platelet count that people are talking about is an interesting observation, but I have no data that correlates to anything. The other way that I look at it as a hematologist is reactive thrombocytosis is generally not considered to be associated with increased thromboembolic risk, whether it's due to iron deficiency or whether it's due to inflammation or anything.

So I'm not quite sure what to do with this. It's also interesting that ET is caused by a JAK2 activator most frequently and this is a JAK2 inhibitor, so how to link all this, I don't know.

So that being said there, then the question is what is venous thrombosis risk. And there, if I go back to Dr. Nair's presentation. And how about
if I go to slide 31?

So this is venous thrombosis and I may need some explanation of where these different numbers come from. But one of the things that I look at in patients on average is that the VTE risk for all of us sitting here is on the average of 1 to 2 per 1,000 people per year.

It goes up as we age. It goes up to 1 in 100 by the time we hit 80. When we're in our 60s, it's probably on the order of a couple, 2 to 3 per 1,000 people.

Now, if I look at things like rheumatoid arthritis and I just did a search in the literature and it looks like, with just rheumatoid arthritis, your risk is increased to maybe two- to two-and-a-half-fold. So if I'm talking about people in their 60s, let's say, they're already at 2 per 1,000, so now I'm making it somewhere on the order of 5 per 1,000.

Now, if I look on this table, if I look across the red bar, there clearly seems to be something that's happening when you go from the 2
to the 4. Now, there is a limitation in the number of patients treated, et cetera. But now you're at 17 per 1,000.

However, when I go down to the 0 to 52, I have 8 per 1,000, which isn't that much different than the general rheumatoid arthritis patient population to begin with. And then I was trying to find the papers that were mentioned earlier. There's two papers in drug safety, which were looking at JAK inhibitors in rheumatoid arthritis as a class.

It seemed that, actually, there are an increased risk of events somewhere on the order of 3 to 7 per 1,000 patient-years. So all these numbers are close to the same other than the fact that, in the first 0 to 16 weeks, you have that 1.7.

I guess my question to Dr. Nair was, are those numbers cumulative as you go down? Is it 5, and then 2 more make the 7, and then no more make the next 7? Or are those -- the 5 is not included in the 7?
DR. NAIR: So the 0 to 16 and then the 0 to 152 are cumulative.

DR. ORTEL: There are two more events over the course of the next X.

DR. NAIR: Correct. The greater than 52 weeks is only events that happened after greater than 52 weeks, so that's not --

DR. ORTEL: So it's an additional 7.

DR. NAIR: Correct.

DR. NIKOLOV: Maybe for further context, we have additional cumulative numbers in the background briefing document table, 6, 7, and 8, I think, 6 and 7, which appears that the numbers keep accruing.

DR. ORTEL: So from this data, I would say that the 2-dose -- I can't say that there's necessarily any increase over what you might expect in the general population of rheumatoid arthritis. It does look like there might be some increase in the 4, although it's relatively modest. If you look at other drugs that are out there, combined oral contraceptives increase the risk three- to
fourfold.

So you're talking about something on the same order, probably a comparable order of magnitude with a different drug. Looking out for it right now, you have nothing. I would say that the platelet count doesn't seem to me to be anything that would predict who's at risk, so it's probably unlinked.

All you can go on is by basically things like what I was asking the sponsor about, whether or not patients with prior VTE were potentially excluded from the trials, things like that. They did identify in one of the figures a couple of risk factors, one being prior VTE, age, and I think BMI was another one that was in there.

So you may be able to identify clinically certain parameters that might predict a higher-risk patient population group. But you can't predict it overall. I always look at it as it ends up being a risk-benefit assessment for patients as far as when I'm putting somebody on a new drug. And I like to make sure that they know what they may have as an
increased relative risk for venous thrombosis and then also what that absolute risk is for these patients.

What is treatment? It's going to be anticoagulant. So I found it interesting that 1 of the 6 patients who had a VTE wasn't treated with an anticoagulant, which I wasn't quite sure about whether the diagnosis was correct or there was a bleeding risk that prohibited that.

But still, you put them on an anticoagulant and the question is, if you stop this drug, you could potentially stop the anticoagulant after 3 to 6 months, considering a provoked event. If you wanted to keep them on this drug, you could and continue the anticoagulant.

So that's kind of my take on this thrombocytosis issue, which I think is a laboratory phenomenon that may be unrelated to any clinical outcome and then the clinical events as far as VTE.

I'm not sure if that clarified anything.

DR. NIKOLOV: This is Nikolay Nikolov, one question to Dr. Ortel.
DR. SCHER: Dr. Nikolov?

DR. NIKOLOV: So most of the data presented here were revolving around DVT and PE. Do you have any comments on the arterial thrombosis? Because they also seemed to accrue throughout the program.

DR. ORTEL: It was harder for me to pull out the MACE data because the numbers seemed smaller, number one, and this is also a patient population that's going to have underlying arterial disease frequently anyway.

So I didn't mention much on that because, to me, I don't think that would be something that would make me decide against or for giving a patient this drug. It's more that the venous events seem to kind of stand out as being something that's more prominent and that's why I focused on that.

DR. NIKOLOV: Thanks. Dr. Boudreau?

DR. BOUDREAU: Hi, Denise Boudreau. To make sure I have this clear, with regards to the 4-milligram dose, we're talking about an indication that is in patients who have failed 2 or more
DMARDs. Correct?

But the safety data here that we're talking about with regards to thrombosis is among all patients. And the numbers are really small, even given that. So we really don't know in the actual population for which this will be indicated. Correct?

Or we can't really look at that data and so it would be too small?

DR. NIKOLOV: So this is Nikolay Nikolov. I think we have some data on the overall safety between these two subgroups, not specifically for the thrombosis events. The applicant might have some information on the thrombosis in these two subpopulations.

DR. McGILL: Let me ask Dr. Veenhuizen if she has that. Looking for the two plus DMARDs. Is that correct, ma'am? That's what you're looking for?

DR. VEENHUIZEN: Right. The single DMARD, the 2 plus DMARD. So we did do some data analysis on these that had a single DMARD exposure or
intolerance, inadequate response, and we have information on those that have intolerance or inadequate response to 2 or more DMARDs.

You can see here this is the data from the weeks 0 to 16 placebo-controlled time period, with the first three columns showing placebo, 2 milligram and 4 milligram, in those patients that were refractory to 1 prior DMARD, and then the next three columns showing those that had failed 2 or more prior DMARDs.

If you go to the second row from the bottom, you can see that we had 2 VTE in that population of 143 patients. When we go to the extended time period, which would allow them more exposure, you can see here again the one prior DMARD group, 2 and 4 milligram, and the 2 or more prior DMARDs group with the 2 and 4 milligram, and again second row from the bottom, which show the VTE incidence rate, just recognizing that these are fairly small populations.

DR. SCHER: Dr. Jonas?

DR. JONAS: Beth Jonas. Let me just go back
and make sure I understand the indication, because I'm reading here on slide number 3 on the FDA briefing the recommended dose is 2 milligrams once daily for patients with an inadequate response or intolerance to more than 1, so not 1 or more, so 2 or more DMARDs. Then a dose of 4 milligrams is recommended. Am I reading that correctly?

DR. NIKOLOV: That's how we read it, too.

DR. JONAS: Thank you.

DR. SCHER: Dr. Katz?

DR. KATZ: James Katz. Has the sponsor divulged any data on the 8- or 10-milligram dose patients that they've treated?

DR. McGILL: Dr. Veenhuizen? I assume you're talking about VTE or general safety? Do you have that, Dr. Veenhuizen?

DR. VEENHUIZEN: There was one pulmonary embolism in a patient in another indication, an 8-milligram dose that was reported. That's the only other DVT or PE that we had reported at higher doses.

DR. SCHER: How many patients were given 8
milligrams?

DR. VEEHUIZEN: Total number of patients that were given 8 milligrams, I'm not sure if we have that data tabulated, but we can work on that and get back to you.

DR. SCHER: Dr. Miller?

DR. MILLER: Don Miller. I have a question for FDA. On Dr. Nair's presentation on slide 22 on serious adverse events, I just want to be sure that I'm reading this correctly. For baricitinib, 2 milligrams, the rate per 100 patient-years was 11.4 for serious adverse events overall; for 4 milligrams, 14.4; yet over on the right-hand side, the difference is 6.1. How does 6.1 get there?

DR. LEVIN: Greg Levin, FDA. So my understanding; these are results reported by the applicant to us based on an information request. We in the past few days have ran some internal analyses and tried to understand a couple of these numbers.

My understanding is that the 4 versus 2 comparison was based on a subset of studies that
had only the 2- and 4-milligram arms, which is
different than the numbers of events and event
rates that are being reported in the bari 2 and
bari 4 columns on the left side of the table, but
I'd actually like to turn it over to the applicant
to indicate whether that's correct, which would
explain potentially why there's slight differences
between the differences in the rates that you would
compute in your head on the left and what you see
on the right, but I'll turn it over to them to
answer that.

DR. BEATTIE: Can you hear me all right?
Okay. Scott Beattie. This is an analysis that we
did per FDA request and they asked us to stratify
the results by the study. So when we compute those
incidence rate differences, then they account for
only the trials that included both the 2-milligram
and 4-milligram dose, hence the differences can be
slightly different than we see from the raw
numbers.

DR. SCHER: Dr. Miller, you have a follow-up
question?
DR. MILLER: Yes. Just following up on that table we looked at, the risk of thrombosis is very important, but on the other hand, you have to look at it in perspective of all the serious adverse events.

It seems like there is a little difference there as well, but it's not huge. And certainly, they're kind of what's expected for a drug like this, so I think I have to keep the bigger picture in perspective as well.

DR. SCHER: Dr. Kim?

DR. KIM: Seoyoung Kim. I have a question for either applicant or the FDA. So we heard a lot about what the potential mechanism of the drug would increase the platelet counts, but I don't think I heard much about potential pathophysiology mechanism for DVT or PE in the treated groups.

So I don't know if that has been explored.

DR. McGILL: We are happy to if you would like. Dr. Krishnan

DR. KRISHNAN: Gary Krishnan, Eli Lilly, discovery research. We have carefully explored the
mechanism of baricitinib, both from the formation of the clot, to the makings of a clot, and the lysis of a clot.

After careful examination, we really couldn't find substantial evidence that would support the role of a JAK1 and 2 inhibitor in supporting these processes. In addition, we've also looked at our two-year carcinogenicity study, which is a lifetime exposure -- not this slide; it's slide PS-11, please, thank you.

In this study, we actually show; we examine specifically at the end of the two-year study the histopathological evidence, both in the arteries and in the veins. And we saw no evidence of thrombus or infarcts in these animals.

Just as a point of reference, other medicines such as diclofenac, the PPAR inhibitor, and also the drug that's used for prostate cancer all show positive in such a two-year study. So this study is capable of detecting thrombus formation and infarct formation. But in our studies, for lifetime exposure, not a single rat
showed this effect.

So collectively, while we did not see evidence, we still continue to believe this is an important risk and we have committed to monitoring this in the geographies where we have successfully approved both 2 and 4. And we are cautiously encouraged by the incidence that we observed in these approved geographies.

DR. SCHER: Thank you. Yes, please?

DR. WHITTAKER: So Matt Whittaker, FDA, non-clinical reviewer. I just wanted to add a quick comment related to the pathophysiology. So my focus in preparing for this meeting was platelet number and understanding how JAK2 inhibition could affect platelet number.

But I will comment that there is some evidence that thrombopoiesis can affect platelet function. And so if we're thinking that the TPO or thrombopoiesis is sort of driving this change in platelet counts, but if TPO levels are changed, then that could also potentially affect platelet function in addition to platelet number.
DR. SCHER: I have many questions, but I guess one of the questions that we're charged to answer and I don't think we're doing as of yet is to try to understand whether or not the data that we have been presented with for 2 milligrams is enough to give us adequacy in terms of safety.

A lot of what we are hearing pertains to the 4 milligrams, but the fundamental question that we have right now that maybe the statisticians can help us understand is whether or not the extent of the data, with the amount of patients we have on the 2 milligrams and the placebo is enough statistically and/or clinically to understand the safety concerns of baricitinib. Maybe Dr. Brittain can help.

DR. BRITTAIN: Obviously, it's not ideal. I mean, already, even with the 4 milligram, when we have more data, at least I don't feel like I fully understand the thrombosis risk. We sort of see contradictory pieces of evidence in different parts of the data.

On the other hand, I don't know if it's
appropriate to consider the results on the 4 milligram as kind of the upper bound for the risk of the 2 milligram. I mean, it's a little bit of a leap of faith there, but at least it gives some more information.

But these are a lot of small numbers, especially on the thrombosis. But I don't see, again, in terms of the difference between 2 and 4, again, all the numbers are small, so it's hard to know, but there doesn't seem to be a clear-cut sign that 2 is much safer than 4.

Maybe in a few tables it looks that way, but I think the numbers are just too small to know. And not answering your question directly, but I did want to pose another question, which is, in terms of the thrombosis, is there any risk factors beyond baseline platelet, which doesn't seem to be related, that could be used to determine patients who shouldn't be exposed to this?

DR. SCHER: Dr. Caplan?

DR. CAPLAN: Liron Caplan. There are 400 total patients in the W and the X study that were
given the 200. And that's just not enough to power these sorts of determinations. And I'm not sure that a phase 3 pivotal study is intended to do that. You're not going to detect a difference in malignancy or TEs just based on the underlying rate.

So the answer is to answer B, I think, at least as far as I'm concerned. It doesn't provide the necessary evidence. I'm not sure it's intended to. At least, I don't think that is. I think, in my mind, the purpose of a phase 3 study is to identify large effect sizes.

So asking about infrequent events in a study that was designed to detect large effect sizes, particularly around efficacy, much less so adverse events, doesn't make sense.

DR. SCHER: I guess, while that is true, one of the concerns that the FDA has is that numerically and within a short period of time, there's a serious side effect or adverse event that can lead to, as Dr. Russell was alluding to, sudden death.
So the question, too, in my mind or some of the questions I have, these being one of those, is whether or not there's a discrepancy between what we're seeing in the 0 to 16 weeks, which is numerically relevant, clinically highly relevant, but also that there's a discrepancy happening elsewhere. So this drug has been approved in Europe. There's post-marketing. There's no signal there.

There seems to be confusion there in terms of at least numbers that we were presented with and we are, at least I am, unclear as to whether or not this type of data has been seen in other programs. Maybe Dr. Nikolov can answer some of these.

DR. NIKOLOV: So this is Nikolay Nikolov. I just wanted to clarify that assessment of safety for pretty much a majority of the clinical development as based on descriptive comparisons. We provide point estimates with confidence intervals around the differences just to give a sense about the uncertainty we have about these differences.
With small numbers, especially for rare events, this is almost impossible to make
definitive conclusions. What we would like the committee to comment on is whether the data are
sufficiently reassuring about the safety of one or the other dose.

I think we made it very clear, very big difficulties analyzing data like this. And it's not because only the numbers are small, but because the design of the program was such that we cannot really make reasonable comparisons for rare events.

This has been a chronic problem for many of these programs. And that's why it's very difficult to do any cross-study or cross-program comparisons to other products in historical comparisons, because they were very, very complex programs like this one and how the events are captured, recorded, and analyzed at the end has so many nuances that it can actually sway the results one way or another.

That's why we have difficulty interpreting the safety from this particular program, where we see a signal with the high dose because we have the more
numbers there.

But we asked the committee to comment on whether the lower dose has sufficient safety information to extrapolate the safety from the higher dose to the lower dose.

DR. SCHER: Thank you. Dr. Russell?

DR. RUSSELL: If I could just offer a little bit of perspective from the medical literature, I have up on my computer a publication that came from Taiwan. It's British Medical Journal and it's dated April 3, 2018. The study was actually done in 2013 and 2014, but just came out in British Medical Journal.

In that paper, what the authors did was to look at the public health insurance program that covers everyone in Taiwan and look at the frequency of thrombophlebitis and pulmonary embolism in rheumatoid arthritis patients.

When they did that, they came up with a frequency of -- they reported the numbers in terms of numbers of patients per 10,000 patient-years. But if we back that down to what we're looking at
here per 100 years, it would be 0.1. And I'm looking at a table, 31, from the FDA form and its rate of 1.7 for Bari 4. That's with 1,000 patients, 997 patients.

So that's a 17-fold increase in the frequency of thrombophlebitis. With this drug, I would see that as not being trivial.

DR. SCHER: So we will take a break if you will allow me to, followed by continuous discussions about this topic, followed by a vote. Is that fair and balanced? Very well. We'll reconvene in 15 minutes. So that would be 3:52.

(Whereupon, at 3:37 p.m., a recess was taken.)

DR. SCHER: Thanks for coming back. We're going to resume our discussion from earlier. I believe Dr. Ortel had a few comments.

DR. ORTEL: Sorry. Tom Ortel. I wanted to follow up on the comments made about the study that was just published about the incidence rate of VTE in the Taiwanese population. And I think that, here, there was a point made this morning by --
DR. SANSING-FOSTER: Dr. Sansing-Foster.

DR. ORTEL: -- Dr. Foster about the important issue of race and ethnicity for baseline VTE rates. And in the Asian population in particular, it's somewhere on the order of 1/5th to 1/10th of what it is in the Caucasian or African populations. So you're dealing with already a population that's about 1/10th to 1/5th of the incidence.

So if you're adding drug on top of that and it's still 1/5th to 1/10th below that, that would actually be expected based on comparable effects of the drug on that patient basal risk. An I think you have to place these studies into context when you're looking at mixing it across patient groups.

DR. SCHER: I thank you for that comment, but if I may steer the conversation a bit more, I think part of the challenge that we're having as a committee is the fact that we are seeing a potentially severe adverse event within 16 weeks of prospective randomized controlled trial data.

We're trying to extrapolate data from
retrospective database-driven articles. Whether they're related to ethnicity or gender, I don't think, is relevant to the overall discussion that we've heard from the FDA.

So the question is that's still in my mind, are these numbers that we see with the 4 milligrams of concern because they are real statistically speaking based on the data that we have provided and whether or not we have the 2-milligram dose safety dataset to conclude whether or not that's relevant for that particular dose. And I'm not hearing and I don't know if this is me, that we have significant evidence one way or another.

Dr. Brittain?

DR. BRITTAIN: So again, for the 4-milligram dose, the evidence about thrombosis is mixed. We see the statistically significant result in the very early time point against placebo. We don't see it in some of the other time points.

Also, I believe the sponsor presented, like, when people just switched over from another arm, it wasn't like, just because you just started, that's
when you get the thrombosis.

So at the same time, it's in the context of this elevated platelets, so we had that, yet it doesn't seem to be related to platelets. So it's all very confusing. It's hard to interpret. There's that.

But as far as the question about the 2 versus 4, after we got some clarification a little bit ago about what these tables are that are in the FDA booklet, the right-hand column is the head-to-head comparison, which we were wondering why so often they didn't seem to match with the result in 2 and result in 4.

I keep flipping back between these pages of the event rates and comparing the 2 to 4 head to head. And while the numbers are small and there's no way to know at all definitively, there does seem to be a general pattern of the 2 being numerically lower than 4 for most of the events listed for what that is worth.

It's certainly true with the platelets. I guess there's no question that there's a dose
response on the platelets.

DR. SCHER: I have Ms. Aronson followed by Dr. Horonjeff.

DR. ARONSON: This is a question for Dr. Whittaker or Dr. Ortel. So if I'm on either 2 milligrams or 4 milligrams and I say I'm going to be taking a 10-hour plane ride, are you concerned if I've just started the medication and my platelets have gone up or is there anything there that there's some real caution in relationship to that TPO overload and then the platelets going up? I just wondered about the timing, too.

DR. ORTEL: I would just say be cautious because you're mixing two different mechanisms for potentially having a thrombotic risk. I don't look at anybody and tell them they shouldn't take that vacation trip to Africa if that's where they want to go, regardless of whatever else they may be taking.

I may give them something, but I wouldn't mix them that way.

DR. WHITTAKER: I would really have a hard
time making any conclusions based on what I've presented today as it relates to the specifics of the timing of the platelet response to the TPO elevations, so I really couldn't comment further on it at this time.

DR. SCHER: Dr. Horonjeff?

DR. HORONJEFF: Hi there, Jen Horonjeff. I appreciate you bring some real-world scenarios into this because, from the patient perspective, we do have to think about these things. And in the absence of any clear data that the 4-milligram has significant risk associated with it, which is just unclear, these patients want these options.

Where it sounds like the 4 milligrams would be indicated in people with refractory cases, to me, those individuals have a different risk tolerance to these types of adverse events anyways. And that's where I just still keep going back to that, having the ability for them to make that decision with their clinician to review the risks and just be able to have that as another modality at their disposal.
DR. SCHER: Dr. Caplan?

DR. CAPLAN: So I had two items. The first is, I'm a little bit confused as to how that last DVT arrived, number 7. Sorry to still be sticking on that, but I find that highly troubling in light of prior episodes that the FDA's been involved with.

I just won't say it's implausible, but it just seems shocking to me that, with all of these probably hundreds of analyses, that formal comparisons of ADEs were not done in terms of infection. That flummoxes me, and I mean by the sponsor, obviously. The FDA did them.

DR. NAIR: If the applicant wants to comment further, I'll explain what my understanding is, that one of the cases was originally coded as a thrombophlebitis and later found to be a DVT. And that's why it wasn't reported in the original submission.

DR. McGILL: Actually, Dr. Veenhuizen, do you want to review those cases? And I think there's some questions about what happened when you
switch drugs as well, so people can see and better appreciate that.

DR. VEENHUIZEN: Melissa Veenhuizen, Lilly. So it is correct and, if you noticed, when we had the slide up on the 6 cases in the placebo-controlled time period, the asterisk at the bottom notes that this was one case number two in the row that was reported as thrombophlebitis by the investigator.

So when this potential risk was brought up, we went back and very thoroughly evaluated all of the safety information, looking at standard MedDRA queries and going in a little bit deeper. And we found that, sometimes, from just a language and a translational perspective, something could be recorded as something like a thrombophlebitis where it was in fact maybe a DVT.

So we thoroughly can vast [ph] the data and that's where that additional case came from. I think of note was the issue that, when we had these patients that switched from the active comparator or from the placebo, we did not see these number of
cases.

One other point I'd just like to clarify -- there was a comment about fatalities. And I think it's important to note that, of the 42 events on baricitinib, one of those was fatal. But also, there was a fatal case of PE on the MTX treatment group. And that was one individual in this particular study and it was not mentioned, but those were the only 2 cases of DVT or PE that were fatal in the entire program, one on baricitinib and one on MTX.

DR. SCHER: Dr. Caplan, does that satisfy your question?

DR. CAPLAN: So are you saying that, that patient with the asterisk is the seventh one? Because there's only 6 there.

DR. BAKER: Yes, and Robert Baker, Lilly, thank you. I think, if we could go back again to the FDA's presentation and look at slides 29, 30, and 31, I think I can explain the discrepancy. So you raised a question, I believe, initially on this slide that said overall
thrombosis and asked why it had seven when we were presenting six. As I mentioned, this is an analysis by the FDA that is combining venous thromboembolism and arterial thromboembolism.

So if you go to slide 30, the comparable number here is two, so there were two arterial thromboemboli going into that count of 7. And then if you go to their slide 31, the number is five.

It's this 5 that Dr. Nair has explained and we agree that the difference between the 5 they've counted and the 6 that we have is that, as we've dug back into this, we have gone and looked for events that were not coded initially as thromboembolism and found the one that was superficial phlebitis that we thought appropriately went here and that added that one. Does that reconcile it?

So the difference between our 6 and their 5 is that case that would be appropriately on slide 31, not the slide that had 7.

DR. SCHER: Does the FDA have further comments about that?
DR. XIA: Sherman Xia from FDA. Actually, I think the difference between 5 and 6 there is because here is 0 to 16 weeks and what the sponsor presented was 0 to 24 weeks.

Originally, this was presented as 0 to 4 and that additional case increased that to five. And the difference between 5 and 6 is because an additional case was between 16 and 24 weeks.

DR. SCHER: So which one is it?

DR. XIA: If you if you open Lilly slides that were just presented with 6 to 0, it shows 0 to 24 weeks.

DR. McGILL: Perhaps this is the one that Dr. Veenhuizen can --

DR. SCHER: I would just let the FDA finish.

DR. McGILL: I beg your pardon. I was just trying to get the slide he asked for.

DR. SCHER: Yes, that's okay, but please --

DR. VEENHUIZEN: No, we agree that the differences -- there was an additional event between week 16 and 24, so that is accurate.

DR. NIKOLOV: This is Nikolay Nikolov. This
just underscores the complexity of the safety
analysis. There are many ways you can slice and
dice the data, many time periods, many ways to
account for the events, whether to censor the first
event or while they were on the dose they're
currently taking.

So differences in numbers are probably seen
even within the FDA briefing document.

DR. SCHER: Dr. Kim?

DR. KIM: Seoyoung Kim. Just to clarify,
the cases or the event number under arterial
thrombosis include MACE like MI or stroke,
thrombotic, ischemic stroke, or are they separate
entities?

DR. NAIR: They do not. The MACE are
reported separately.

DR. VEEHUIZEN: If I could clarify, if we
could have slide AT-6, this shows what qualified as
an arterial thrombotic event from the sponsor and
what we provided to the FDA.

These are the search terms that were
included and you can see here ischemic stroke,
myocardial infarction, along with TIAs over on the right-hand side, and CVAs were included, all of which would be a subcomponent of a MACE.

DR. KIM: So it is potentially part of it.

DR. VEENHUIZEN: Yes.

DR. SCHER: Dr. Ortel?

DR. ORTEL: Tom Ortel. If I look just at your first question there, A, adequacy of the safety database, getting at what you're asking us, I would look at it and I'd say, if I look at the 4 and I'm trying to show that there's a statistically significant increase in thrombotic events compared to baseline, I'm barely able to do it with the numbers that I've got there.

The 2 is woefully underpowered. So I think that I'd let the statisticians speak up instead of me, but I'd just look at it as, based on knowing what the basal rate is in the population, you don't have enough data to answer that question.

But conversely, I don't think the study was powered to look for that. And that's where I think Dr. Caplan had mentioned that earlier. That's
where you're getting into this problem of, it's not powered to capture all of these small events, so A, I would say, if I just look at it from a statistical standpoint, I'd have to say no.

DR. SCHER: I appreciate that because it clarifies some of our questions. Now, can you expand on the 4 milligram comment that you just made? You were certain that you can answer the statistical question. Is that what I understood for the 4 milligram?

DR. ORTEL: So the 4 milligram question isn't in this list. You're just asking if there's a difference between 2 and 4.

DR. SCHER: It's C. It's all the way down.

DR. ORTEL: Right. But it's not asking specifically is the 4 -- it's not quite phrased the same way, is what I'm getting at. But I can say that, in 4, you do have at least a signal. In 2, when I look at the 0 to 16 weeks, there was a 0 number of events, so I can't even say anything about that.

You do have a signal on the other. You had
997 patients. You had 300 patient-years. I'm looking at figure 31 or page 31 on Dr. Nair's response or presentation. That's the one that gives you some idea of the numbers of patients.

DR. SCHER: Can we pull up that table, please?

DR. ORTEL: 31, venous thrombosis, if I'm just looking at that one again, so it gets confusing when you start saying combined and everything else. So you can see on there, if the incidence rate of venous thrombosis in the general population is 2 in 1,000 and I've got only 140 patient-years for bari 2, I'm nowhere near there. At least I've got 298. I've got a total of 1,000 patients enrolled in that 4, so I'm getting close to where it might be statistically significant.

But the bari 2, to your first question, I'd have to say no. The second one, I'd say, okay, you've got some signal there, you've got something there. But again, from a statistical standpoint, I don't think it was powered. If I was trying to power it to tell a difference in the outcome event,
I don't think it's got the power to do that.

DR. SCHER: I guess I want to clarify that point. I think it's very, very relevant. None of these studies are powered to look for rare events. And so if the FDA can, expand on that.

DR. NIKOLOV: Right. So this is Nikolay Nikolov. The phase 3 programs are generally designed to demonstrate efficacy and safety as descriptive. Again, for rare events, it's really the totality of the data that we look at, we're not looking for in the statistical comparisons.

If we see statistical differences, that certainly means a lot more than a few numbers. What I wanted to ask the committee also to consider is if we consider this a signal and the applicant is also concerned about this to the extent that they propose to include it in the warnings and precautions.

My question to the committee is, do you believe that, if real, this signal is acceptable in the overall risk-benefit assessment for one or the other dose in addition to the rest of the safety
issues that we discussed?

DR. SCHER: Dr. Kim?

DR. KIM: Seoyoung Kim. So the patient could be switched from placebo to bari 2 or from bari 2 to bari 4 I guess after week 16. So my question is, for the two bottom rows, the set of rows, so for example, bari 2, where there are 2 cases between 0 to 52 weeks, are they listed under bari 2 because they were randomized to bari 2, or they were rescued to bari 2, or bari 2 was at the time of the event, and similar to other cells? Is it their assigned treatment at the beginning or that's the treatment they are taking at the time of the DVT event?

DR. NAIR: This is Raj Nair, FDA. This analysis should have been where they were on the dose and stayed on that dose. There was no switch, no rescue, no escape. So someone who was on a 2-milligram dose of baricitinib would have started on 2 milligrams of baricitinib. Someone on 4 milligrams of baricitinib would have started on 4 milligrams of baricitinib.
Then if there was an escape or a switch, those events would not be included.

DR. SCHER: Dr. Russell?

DR. RUSSELL: Russell. I got the impression from the reading that the venous thromboembolic events occurred early in the course of therapy. Could the sponsor address that? Is that true?

DR. McGILL: Dr. Veenhuizen?

DR. VEEHUIZEN: So in the core presentation, what we showed was a Kaplan-Meier plot of the time to event onset. And I believe I had mentioned that these occurred anywhere from 37 to 1,658 days. And what you actually see here is that they accrued at about 5 percent annually.

This is similar to what we've seen in accrual for other events like MACE, for example. And so there was not any temporal relationship to the starting of baricitinib treatment showing that they were essentially clustered, some of them much later in the time course.

There was much greater association with the presence of risk factors. Then there was the
treatment with baricitinib.

DR. RUSSELL: So were the patients taken off the medication if they had an event?

DR. McGILL: She's answering.

DR. VEENHUIZEN: I'm sorry. Just to clarify, that was 0.5 percent annually if I had misspoke. I believe the question was what happened as far as baricitinib continuation relative to the 42 patients. We did evaluate. There were at least 28 of those that continued on baricitinib treatment.

Some of them had temporary interruptions. I know we have a slide on this if we can get to it. But many of them had a temporary interruption and then further continued on baricitinib. 12 of the total events occurred after the patient had discontinued from baricitinib out of the total of the 42.

So continuation was actually frequent because 28 of those patients that had events -- 40 were treated with an anticoagulant. Two did not receive any anticoagulant therapy and both of those
patients continued treatment with baricitinib.

One recovered. The other, we had a report that there was no worsening and no further DVT. 28 of the 42 total events were serious, 5 permanently discontinued, and of the 28 that continued therapy, 2 had a recurrence.

DR. SCHER: Follow-up on that; isn't every DVT event a serious event? I am asking to clarify.

DR. VEENHUIZEN: That's a very good question and we might ask Dr. Dorner to comment on this as well, but patients would be experiencing these events and, as you saw, some were treated with anticoagulants and some were not, but these were serious as reported by the investigator.

Generally, that meant that there was hospitalization or something that required incapacity or further treatment, so no, not all of these cases were serious. And that's one comparison that's difficult when we look at our data compared to other registration programs.

For example, all we were able to find was the report of serious, those that required
hospitalization. But I'll ask Dr. Dorner to comment on how these are treated in clinical practice.

    DR. DORNER: Thomas Dorner. I'm a rheumatologist at Charite University in Berlin, Germany. I'm also a hemostaseologist, and I'm leading a coalition, a consultancy group for a 3,000-bed university hospital.

    I'm also part of the thrombosis safety advisory committee and we carefully also evaluated all of these 42 individual cases. And as some of the panel members already alluded to and very consistent with the multivariate analysis, the main risk factors are the common risk factors that are also happening based on an enhanced risk that patients with rheumatoid arthritis have.

    This is at the lower end. We are also seeing in rheumatology practice a number of other diseases like connective tissue diseases, vasculitis, antiphospholipid syndrome, with a vastly higher or substantially higher risk for thrombosis events.
The main risk factors so far that have been identified, the classical ones, prior DVT, venous thrombotic event, enhanced BMI, enhanced age, and the additional risk factor of COX-2 inhibitor usage, which was one of the data of the multivariate analysis.

DR. SCHER: Thank you. Dr. Nikolov?

DR. NIKOLOV: I have one quick question, if I can, to the applicant. This refers to the Kaplan-Meier curve that you just presented. Do you have the same Kaplan-Meier curve for the two doses, 2 versus 4?

DR. VEENHUIZEN: We do have that information. If we could have that slide come up, I'll be happy to speak to it. So here, you can see the event accrual frequency over time. On the bottom of this graph, you can see 0, 12, 24. This is time in weeks. And you can see that there is a separation in the doses in the first 24 weeks, yet over time, they seem to grow greater or closer in alignment with accumulation of events.

Then this doesn't necessarily show clearly
how the exposure adjusted outcomes by dose, which was demonstrated in the slides that I presented, because this is cumulative rather than showing an overall incidence rate on a patient-years exposure standpoint.

DR. NIKOLOV: Thanks.

DR. SCHER: Dr. Brittain, you had a last comment. And then I had a question to the FDA.

DR. BRITTAIN: My question -- and maybe there is no answer for this -- I mean, is just my trying to understand it. We see some signal with the thrombosis. We see a clear effect on platelets, but you don't see at an individual level a connection between platelets and who has the events.

That just seems hard to understand. Does that seem mysterious or not?

DR. NIKOLOV: This is Nikolay Nikolov. Again, there is no clear correlation between the platelet counts and the thrombotic events. And that might be just a red herring that both co-exist, but that's certainly an observation of a
potential signal of thrombotic events regardless of the platelet counts.

DR. BRITTAINE: I mean, it could be since they're maybe all kind of uniformly elevated, that puts that group at a bigger risk. There wouldn't necessarily be a correlation, I guess.

DR. NIKOLOV: Yes. I don't think we can speculate on this, but that's one of the reasons we invited also a hematology expert on the panel. Hopefully he can enlighten us.

DR. ORTEL: Tom Ortel. So just to follow up on that, a number of years ago, thrombophilias were first found and people started looking for them and started checking everybody. And what we've learned over time is that, really, those don't help very much in evaluating the individual patient.

In fact, most people with factor V Leiden probably die of old age when they get run over by a truck or something like that. They don't ever have a clot. So there are a number of variables.

One of the hypotheses that was brought up by the FDA was that maybe the platelets are also more
active. That's very hard to measure and assess. So not only an increment in number, but maybe an increment in active platelets, if you will.

But that is difficult to assess and nobody has linked that to an increased risk of venous thrombosis. So that's why I urge caution in trying to link a laboratory phenotype with a clinical phenotype.

DR. SCHER: So last point; we are short in time. So you alluded to the fact, Dr. Nikolov, that one question to the committee is the potential for it to include or think about including a warning or precautions or a box sign in terms of thromboembolic events. What are the other options that we should be considering when taking into account all these data?

DR. SEYMOUR: This is Dr. Seymour. I think our main tool we have is to maximize labeling to communicate any safety risks. Certainly, a boxed warning is our highest level of safety warning. I think the applicant has currently proposed having a warning about thromboembolic events.
Beyond that, we have other risk mitigation strategies, but I think we would not want to steer you to go down the pathway of suggesting that the risk mitigation strategy is going to help move the risk-benefit assessment. So I would urge you to continue your deliberations, and discussions, and votes on the risk-benefit assessment and whether this risk is acceptable for this benefit, for this product.

We can use the tools we have in terms of labeling or other risk mitigation strategies to then address that.

DR. SCHER: One very brief comment so I can summarize and move on.

DR. ORTEL: Tom Ortel. So therefore, to follow up on that, the concept is one of -- I think that arguing that there does seem to be some increased evidence or evidence suggesting an increased risk of venous thromboembolic events on these people.

Whether or not it's statistically significant or not, I can't tell you based on the
data that you've got there. But to make the
provider and the patient aware of that before
prescribing it, I think, would be very important.

DR. SCHER: Very well. So I will summarize
if I can again. So I guess the issue at stake here
was to discuss what are we facing in terms of
potential issues of interest in terms of safety.
Dr. Russell began the conversation noting that a
DVT and PE is often potentially fatal in terms of
outcomes. Dr. Ortel described and discussed the
idea that platelet counts based on these data
cannot be used as a biomarker for thrombosis.
That's been repeated over and over again. We don't
have data to support that.

Dr. Ortel also discussed the idea that there
is a lack of data from the sponsor showing what
would occur in patients that have higher
proportions of platelet counts over 450.

But certainly, the platelets don't predict
outcome. That's what we came to the conclusion
about. Now, there was a strong discussion and yet
confusing at times about the fact that we cannot
compare population data with data on randomized clinical trials when it comes to incidence rates of DVT and PE.

Dr. Boudreau essentially mentioned the fact that we truly don't know if 2 milligrams based on the data we have is safe. Dr. Katz asked a question about whether the 8- and 10-milligram dosing had any effect on DVT and PE. And the answer seems to be unclear. There was one DVT or PE event with no denominator.

I think Dr. Russell pointed out a recent study in Taiwan was reported by Dr. Ortel in that there was an issue about ethnicity. And Dr. Caplan pointed out this notion that there was an emergent 6th case or 7th case of a DVT. We did not have a clear description from anybody, actually.

In terms of the question about adequacy of safety for the 2-milligram dose, Dr. Ortel described briefly the notion that the 4-milligram dose has a clear signal, that there is no difference just because the studies have not power to look at those differences and certainly this
notion that the 2-milligram didn't show that effect certainly because of this low number of patients.

The last point was whether or not there's a differential safety profile between the 4-milligram and the 2-milligram. Dr. Brittain said clearly that there's a general pattern that 2 milligrams is numerically lower and, still, we don't have the answer on that, either. And I just wanted to recognize Jennifer Horonjeff with this idea that, from the patient perspective, having more options and having a range of dosing is highly relevant.

Did I miss anything? Very well. So question number 5; are the safety data adequate to support approval of baricitinib, 2 milligram once a day for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. If the answer is no, please ask what data is needed.

(Voting.)

DR. SCHER: Has everyone voted? We're missing one vote? Good to go? All right. As
expected. So I continue with my punitive actions. For the record, by the way, the voting results?

DR. WANG: For the record, for question 5, we have 9 yeses, 6 nos, 0 abstains.

DR. SCHER: We will ask Dr. Caplan.

DR. CAPLAN: I voted no. This was very, very difficult. And I just feel like there are a total of 400 patients who were given this drug at the low dose. And to me, that just isn't enough for me to feel comfortable.

I'll also say and probably reiterate this with the next round, too, that it's a little perplexing to me that, when the signal was detected, whenever this was, a year and a half ago, the decision was made to go to -- and I say this as a pharmacoepidemiologist -- a hypothesis-generating or pharmacoepidemiologic approach to justify this, which doesn't add anymore placebo patients.

So it doesn't add any more clarity. I understand that folks were followed longer for more time. But the crucial amount of time, the clean time, and what distinguishes an RCT from a
pharmacoepidemiologic study, that there's no more
data on that.

So in my mind, it's not clear to me that
we're making any different decision than was made a
year and a half ago.

DR. SCHER: Thank you. Dr. Russell?

DR. RUSSELL: Russell. I would echo that if
I could say it all.

DR. KIM: Seoyoung Kim. I voted yes,
although I wish I could see more data, but I also
understand the trial is not powered to detect the
safety signal, so I voted yes.

DR. MILLER: Don Miller. I voted yes, very
difficult decision. I looked at the overall
serious adverse event rates between baricitinib, 2
milligrams, and placebo. And they were similar.
And this would be used in patients who would
tolerate maybe a little higher risk, but I thought
my best guess is yes.

DR. BRITTAIN: Erica Brittain. I voted yes.
I could have definitely voted no. It was almost a
coin flip; it was a coin flip, basically. So it's
a very uncomfortable yes.

I guess the only justification for voting yes that I had was that, when I look at the 2 versus 4, generally there's some slight indication that the 2 was better than the 4. And so I'm looking at 4 as sort of an upper bound, with the two being perhaps a little better than the 4. So I'm kind of borrowing from the 4, although I'm not even sure the 4 is okay. So that's why the whole thing is kind of a house of cards and I could have gone either way.

DR. ARONSON: Diane Aronson. I voted no for a couple of things. I thought there was a serious signal for patients in this population for thrombotic events. And I don't think that there was adequate numbers of patients or patient-years on this 2-milligram arm that the FDA reviewed and presented. So that's the main reason why I voted no.

DR. HORONJEFF: Jen Horonjeff. I voted yes, although this one was more difficult because of how the indication seems to be that it's saying, if
they failed methotrexate, not necessarily that they
failed multiple others. So I'm less comfortable
with this on based on that this could be the next-
line treatment for them.

So given that, it was a somewhat
uncomfortable yes for the 2 milligram.

DR. JONAS: Beth Jonas. I voted no. Again,
I thought this was really, really hard and I think
most people felt like this could have been a bit of
a coin toss, but if I really look at the numbers
and look at the data that we have in front of us, I
think we just don't have enough information to say
that we're satisfied with these safety numbers.

DR. BOUDREAU: Denise Boudreau, and I voted
no, also with the recognition that this trial
wasn't really set up to answer this question and
the sample size isn't adequate to answer this
question.

DR. SCHER: Jose Scher. I voted no. The
question was about whether or not there was
adequate safety data for the 2 milligrams. And the
answer is scientifically no. Beyond a lack of
rigor in terms of statistically significantly adequate numbers is this notion that this is not any side effect or adverse event.

This is DVT and PE. The mortality rate is anywhere from 10 to 30 percent. The recurrence rate is high. And the fact that the first manifestation of it be at times quite often. A sudden death is not a trivial signal.

Therefore, I would urge the sponsor to get as much data as possible on the safety side.

DR. OLIVER: Alyce Oliver. I voted yes. I agree with what Jose was saying, that the question or the reason I had a difficult time deciding was because of the word adequacy. It was not adequate, but again, with the discussion that we had, it wasn't powered to do so. So I voted yes.

DR. KATZ: James Katz, and I voted yes. I have no comment.

DR. BILKER: Warren Bilker. I voted yes. The current studies weren't designed to detect small signals like this with appropriate power. And clearly, additional data is needed for the 2-
milligram dose to assess the safety profile. But I feel that this can be done with mandated post-marketing studies.

DR. ORTEL: Tom Ortel. I voted yes primarily because of the fact that I agree completely this was not powered to answer the question, but it does raise the question, I think, for the FDA from the perspective of, it seems to suggest that we could have a shifting bar of what we expect somebody to prove if all of a sudden we get something that suggests there might be a signal in something that's a rare event.

That's what concerned me and that's why, the way that this was worded, I decided to vote yes.

DR. IWATA: Soko Setoguchi. I voted yes and I also agree that the studies are not powered to answer the question. This does not, however, exclude that need for careful post-market analysis as well as the label suggestion. And I would not assume 2 milligrams is safer than 4 milligrams, either, because we still don't have enough data.

DR. SCHER: Very well. Question number 6;
are the safety data adequate to support approval of baricitinib, 4 milligrams once a day, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate.

If your answer is no, what is the data that you think is needed?

(Voting.)

DR. SCHER: Voting results for the record?

DR. WANG: For the record, question 6, we have 5 yeses, 10 nos, 0 abstain.

DR. SCHER: I'm less punitive now. It's the end of the day and I may ask Dr. Setoguchi Iwata to start, please.

DR. IWATA: Thank you so much. This was the hardest question for me. So again, that study is not powered to answer the question about safety. However, there is a clear signal about the risk of DVT in the 4 milligram, which I felt that we needed to investigate more.

In terms of the data we need, I think one of
that is the post hoc analysis done using databases where all the patients are coming from U.S. and then this data from trials are actually from multiple countries.

So I think we need to kind of try to separate that, especially knowing that the U.S. population has a higher risk of DVT.

DR. ORTEL: Tom Ortel. On this one, I switched. I voted no. The primary reason was, I had more patients enrolled in this one than I had a signal that I could see. It did suggest that I needed something further to work on. So from a power standpoint, it made me more concerned.

DR. BILKER: Warren Bilker. I voted no. I felt that the signal was strong enough to warrant a no.

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

DR. OLIVER: Alyce Oliver. I voted yes. I was trying to be consistent with my earlier vote. I do agree that there is a signal with the 4 milligram, but the hope is that this would be used in patients who have refractory RA to multiple
biologics and DMARDs.

DR. SCHER: Jose Scher. I voted no. I guess made my case clear, but particularly in 4 milligrams, the signal is significantly more robust when it comes to a severe adverse event.

DR. BOUDREAU: Denise Boudreau, and I voted no for similar reasons that have been stated.

DR. JONAS: Beth Jonas. I voted no. I think the signal is clear. It's not really clear what underlies it, so we may be able to explain the signal in some way with some population-based data or understanding the population of patients that we're looking at, but we don't have enough information to be confident. So I voted no.

DR. HORONJEFF: Jen Horonjeff. I voted yes for this one. Again, consistent with saying that this is going to be for those refractory cases and that they may have a higher risk tolerance for these kind of events if they failed other DMARDs.

DR. ARONSON: Diane Aronson. I voted no. And as far as what data would be needed, I noticed, too, in the FDA evaluation there's an interest in a
controlled clinical trial to evaluate safety risks with two doses large enough to capture safety events such as CV or opportunistic infections, thrombosis, and malignancy. I notice that herpes zoster is higher, too, than the placebo.

So I’d also liken the presentation, the list of exclusions, to be really clear and the list of other concomitant meds that were allowed during the course of the trials.

DR. BRITTAINE: Erica Brittain. I voted no; also again, very close call. I guess just, again, things in general seemed a little worse for the four even though we had more data. Perhaps the safety would be adequate. I guess it gets kind of to the risk-benefit question when we’re talking about certain kinds of patients perhaps.

I did just want to make a general comment, not so much about this particular question before. Some people had said, gee, we can’t expect a study to have power to detect rare events, which of course is true.

None of these studies have power to detect
rare events, but we're frequently, with these studies, I mean, these meaning any FDA studies I've seen, frequently in this situation where we see some kind of signal for some safety event which was not anticipated, so there was no power; the study wasn't designed to detect it. So there's nothing unusual about this. We're in this kind of difficult situation with small numbers all the time, at least in my experience.

DR. MILLER: Don Miller. I voted no. Like Dr. Ortel, I switched my vote because the signal was a little stronger for safety issues here. What to do next; I guess, just getting more data for maybe another comparative trial between doses, looking at safety in particular.

DR. KIM: Seoyoung Kim. I voted no. Again I also changed the answer here to no, mainly because I just couldn't discount the signal that I was seeing with the 4 milligram.

DR. RUSSELL: Jon Russell. I voted yes because I felt the company did a better job with this dosage, understanding the signal and getting
information about the signal, and clearly showed that the drug is efficacious in resistant rheumatoid arthritis. And rheumatoid arthritis is a devastating disease. Organs are being destroyed, joints as organs, and it's war.

We need to make the patient aware that it's war and then fight it like it is.

DR. CAPLAN: So I thought I voted no, but in fact it showed up as yes. I was trying to be consistent, so that should be a no and I apologize.

DR. SCHER: Could you state your name for the record?

DR. CAPLAN: Liron Caplan. Sorry.

DR. SCHER: We enter the matrix now and we can't change it. Could it be noted for the record, though? I'm also reminded that Dr. Iwata should state her name for the record and vote again, just verbally. You have to state your name for the record. I'm sorry.


DR. SCHER: This is what happens at 5:00
p.m. at the FDA. So question number 7, is the
benefit-risk profile adequate to support approval
of baricitinib, 2 milligrams once daily, for the
proposed indication of the treatment of adult
patients with moderately to severely active
rheumatoid arthritis who have had an inadequate
response or are intolerant to methotrexate? If no,
what data are needed? Please do state your name
after your vote so we don't have to go back.

(Voting.)

DR. SCHER: Voting results for the record?

DR. WANG: For the record, question 7, we
have 10 yeses, 5 nos, and 0 abstain.

DR. SCHER: We're going to resume with
Dr. Caplan so he doesn't change his vote.

DR. CAPLAN: Jose, eventually you're going
to have to apply for a grant. I voted no. I just
didn't feel like there was any additional data or
new data on top of what we had previously.

DR. RUSSELL: Jon Russell. I voted no.

DR. KIM: Seoyoung Kim. I voted yes to be
consistent.
DR. MILLER: Don Miller. I voted yes to be consistent with my votes on efficacy and safety. If I was going to be a patient on this drug, I would want to take the 2-milligram dose.

DR. BRITTAINE: Again, since I tossed the coin on the --

DR. SCHER: Would you state your name for the record?

DR. BRITTAINE: I'm sorry, I'm sorry. Erica Brittain. I voted yes. I had to check. Again, since I tossed the coin on the safety vote before, I decided just to keep the same coin.

DR. ARONSON: Diane Aronson. I voted no for the reasons that I previously stated.

DR. HORONJEFF: Jen Horonjeff. I voted yes, but with the caveat that I wish there was an indication after they had failed other biologics.

DR. JONAS: Beth Jonas. I voted no. I just felt like I was confident in the efficacy, but if I was not confident in the safety that I could not vote yes, although it pains me.

DR. BOUDREAU: Denise Boudreau, and I voted
yes, but I would like to see more safety data on
both the 2 and the 4 milligrams.

DR. SCHER: Jose Scher. I voted no for the
reasons I stated before. Again, just to reiterate,
this is an issue that could have been solved if we
had enough statistical data. We interpreted the
data both ways, but if we had the data, then we
will be analyzing data.

Because we don't have enough data, then
we're left with opinions and, in this case, I can
vote based on an opinion.

DR. OLIVER: Alyce Oliver. I voted yes. I
agree with Jennifer that it'd be nice if it was for
biologic failures. I think methotrexate failure
alone is not enough.

DR. KATZ: James Katz. And I voted yes.

DR. BILKER: Warren Bilker. I voted yes,
but I think there should be mandated post-marketing
studies if approved.

DR. ORTEL: Tom Ortel. I voted yes to be
internally consistent and I agree with the concept
of having additional studies post-marketing
DR. IWATA: Soko Setoguchi. I voted yes and I would like to see more data, a clear risk management plan, as well as labeling about informing the risk to the patients and clinicians.

DR. SCHER: This will be question 8, and final question. Is the benefit-risk profile adequate to support approval of baricitinib, 4 milligrams, once daily, for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have an inadequate response or are intolerant to methotrexate. If the answer is no, what data are still needed?

(Voting.)

DR. SCHER: So voting results for the record?

DR. WANG: For the record, question 8, we have 5 yeses, 10 nos, and 0 abstain.

DR. SCHER: I am applying for a grant, so we're going to start with Dr. Setoguchi Iwata.

DR. IWATA: Soko Setoguchi. I voted no to be consistent. In terms of what more data are
needed, I think the signal has to be proven, yes or no. I mean, potentially another trial is kind of showing -- I mean, it is possible that the signal came because of just the imbalance in the patients' group.

Again, I think we have to know if this is more related to causality or just a coincidence.

DR. ORTEL: Tom Ortel. I also switched to no or I switched to no on this one for the same reason, for the safety data. I agree. I think that additional data would be helpful to evaluate this, to know are those VTE events that are being seen truly related to the drug or other things.

The data as collected right now is almost case series as far as the descriptions of the VTE patient population.

DR. BILKER: Warren Bilker. I voted no. I felt that the benefit-risk profile for this dosage was inadequate. It may be that the risk-benefit ratio is appropriate for a subgroup, for instance, those who have failed 2 or more DMARDs, but additional data would have to be collected to
warrant that.

    DR. KATZ:  James Katz. I voted yes.

    DR. OLIVER: Alyce Oliver. I voted yes, but
we need more numbers.

    DR. SCHER:  That would be me, Jose Scher. I
voted no.

    DR. BOUDREAU: Denise Boudreau. I voted
yes. Some things that swayed me were that this is
a refractory population, that there is a baseline
risk in the RA population in general and that the
events that were seen were consistent over time;
they weren't happening all at the beginning.

    DR. JONAS: Beth Jonas. I voted no again
for the same reasons. If I'm not comfortable with
the safety data, then I think that that's really
important. The other thing is that we are asked
about an inadequate response or intolerant to
methotrexate.

These were not the patients that we think we
might actually take that risk on, those patients
with more refractory disease, so based on the way
that was worded, I voted no.
DR. HORONJEFF: Jen Horonjeff. I voted yes, but I took some liberty with the phrasing of the question based on the fact that this is proposed to be indicated for the refractory cases, especially with some of the data looking at the speed at which it was shown to be working as well as then that you could step down to the 2-milligram sort of factored into how I thought about this.

DR. ARONSON: Diane Aronson. I voted no. The term perhaps that might be appropriate for a select group of patients is something that I kept thinking about and didn't have enough information to really get there.

DR. BRITTAINE: I voted no; again, hard choice; to be consistent. Yes, I'm sorry, Erica Brittain. I voted no --

DR. SCHER: You beat me on that one.

DR. BRITTAINE: -- to be consistent with my past votes. But I think that it is possible that the refractory subgroup would do better with four, but we don't really have clear evidence of that. And I would think at least if for some reason the
four got approved, I would hope there would be some algorithm that could be set up, that you start with 2 and then move up if you really need it.

    DR. MILLER: Don Miller. I voted no. Again, I think that the risk-benefit ratio may be less good here. If there is a safety issue, it's more likely to be a problem with a 4-milligram dose.

    DR. KIM: Seoyoung Kim. I voted no. I think we need more placebo-controlled data for this signal and having just more time for the longer duration of the drug treatment may not be that helpful because I think there's also concern for depletion of susceptible as the treatment duration goes on. So that's the reason.

    DR. RUSSELL: Russell. I voted yes. I am sure that there is more data to come.

    DR. CAPLAN: Liron Caplan. I voted no. And I voted no because I felt that was the mandate or the paradigm that we were operating under with potential justification for refusal to approve being insufficient information about the drug to
determine whether the product is safe for use. And then since is the last part, I'll also say this is a classic example of what happens when we don't have enough time in placebo and we have crossover.

I think, although it's raised as an ethical issue, you can't keep patients on placebo for so long. We still have this obligation to first do no harm and these types of questions are almost never answered in the post-marketing data. And so for me, that's what it would require, just more data. And I think this drug has the potential to do good.

But I just need more data to be able to support that.

DR. SCHER: On that note, we managed to be really on time. This is the second time in my life, the first one being my wedding. So does the FDA have further comment? We know we didn't make your life any easier.

DR. NIKOLOV: Yes. We're not here to have our lives easier anyway. But first, I just want to share the FDA's appreciation of your participation in the very vigorous discussion today. It was very
helpful for all of us. We certainly did get a lot of important feedback and input.

The objective was not to keep you as late as 5, but I just wanted to ask a couple of questions if you're okay, before we conclude. So I think we're okay.

DR. SCHER: 60 seconds.

DR. NIKOLOV: We don't want to go past 5:00. But again, we really appreciate you coming here, taking time off your busy schedules, and appreciate your discussion and input. And we're looking forward to seeing you again.

Adjournment

DR. SCHER: Thanks very much, panel members. Please take all personal belongings with you, as the room will be cleaned later today. All materials left on the table will be disposed of, including your Diet Cokes. Please also remember to drop off your name badge and thank you very much.

(Whereupon, at 4:57 p.m., the meeting was adjourned.)