FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (GIDAC) MEETING

Thursday, March 8, 2018

8:00 a.m. to 3:37 p.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. RAUFMAN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Theresa Eisenman. If you are present, please stand.

My name is Jean-Pierre Raufman. I am chief of gastroenterology and hepatology at the University of Maryland in Baltimore, and I'd like the other folks around the table to please introduce themselves starting with Dr. Levine.

DR. LEVINE: I'm Douglas Levine, the industry representative.

DR. PROSCHAN: I'm Michael Proschan. I'm a mathematical statistician at NIAID.

DR. GRAYSON: I'm Mitch Grayson. I'm professor and chief of the Division of Allergy and Immunology at Nationwide Children's Hospital, The

Ohio State University.

DR. FUSS: Ivan Fuss. I am at the National Institutes of Health with expertise in immunology and peds gastroenterology.

DR. JONAS: I'm Beth Jonas from the University of North Carolina Chapel Hill. I am the interim chief of the Division of Rheumatology, Allergy, and Immunology, and I practice clinical rheumatology.

DR. LANE: My name is Cliff Lane. I'm the clinical director for the National Institute of Allergy and Infectious Diseases at the NIH.

MR. MATSON: I'm Tracy Matson. I'm the patient representative from Little Rock, Arkansas.

MS. McVEY HUGICK: Good morning. I'm Joy McVey Hugick. I'm a public health policy and communication consultant, and I'm the consumer representative. I live in Atlanta, Georgia.

DR. STRATE: I'm Lisa Strate. I'm a gastroenterologist from the University of Washington in Seattle.

DR. PARDI: I'm Darrell Pardi, professor of

medicine and vice chair for the Division of Gastroenterology and Hepatology at the Mayo Clinic in Rochester.

DR. FAJICULAY: Jay Fajiculay, designated federal officer for the Gastrointestinal Drugs Advisory Committee, FDA.

DR. LEBWOHL: Benjamin Lebwohl, director of clinical research at The Celiac Disease Center at Columbia University, New York, gastroenterologist.

DR. CHANG: Hi. I'm Lin Chang, gastroenterologist, vice chief of the Division of Digestive Diseases at UCLA.

DR. KHURANA: I'm Sandeep Khurana. I'm medical director of liver transplant, Geisinger healthcare system.

DR. LIGHTDALE: I'm Jenifer Lightdale. I'm division chief of pediatric gastroenterology at UMass Memorial Children's Medical Center at the University of Massachusetts.

DR. JIMENEZ: Sara Jimenez, mathematical statistician, FDA.

DR. HANES: Dr. Lesley Hanes, medical

officer in the Division of Gastroenterology and Inborn Errors Products at the FDA.

DR. ALTEPETER: Good morning. I'm Tara Altepeter. I'm a pediatric gastroenterologist, and I'm the clinical team lead for the application from DGIEP at FDA.

DR. GRIEBEL: Good morning. I'm Donna Griebel. I'm the director of the Division of Gastroenterology and Inborn Errors Products at FDA.

DR. RAUFMAN: Thank you.

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

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

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Dr. Jay Fajiculay, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government

employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest rules, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflicts of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the service 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 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of supplemental and new drug application 203214, supplement 18, Xeljanz, tofacitinib tablets submitted by Pfizer, Inc. for the treatment of adults patients with moderately to severely active ulcerative colitis who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine, or TNF inhibitor therapy. This is a particular matters meeting during which

specific matters related to Pfizer supplemental 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, conflict of interest waivers have been issued in accordance with 18 USC Section 208(b)(3) to Drs. Benjamin Lebwohl, Darrell Pardi, and Jean-Pierre Raufman. Dr. Lebwohl's waiver involves his ownership of shares in a health sector mutual fund. The current aggregate value is between $200,000 and $300,000.

Dr. Pardi's waiver relates to his employer's current study with a competing firm on a competing product. His employer receives between $0 to $50,000 per year. Dr. Pardi does not receive any personal remuneration or salary support from this study. Dr. Pardi's waiver also involves his participation as an advisory board member in a competing firm for which he received $5,001 to $10,000.

Dr. Raufman's waiver addresses five of his employer's current research contracts with three

competing firms for which his employer receives between $0 and $50,000 per year for each contract.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisorycommittees/ committeemeetingmaterials/ drugs/default.htm. Copies of waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035 in Rockville, Maryland 20857, or requests may be sent via fax to 301-8827-9267.

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. Douglas Levine is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Levine's role at this

meeting is to represent industry in general and not any particular company. Dr. Levine is an independent pharmaceutical consultant.

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

DR. RAUFMAN: We will proceed with the opening remarks from Dr. Tara Altepeter.

FDA Introductory Remarks - Tara Altepeter

DR. ALTEPETER: Good morning. My name is Tara Altepeter, and it is my pleasure to welcome everyone this morning. First, I would like to thank all of the members of the committee for taking the time this morning to participate in this

important discussion regarding the risks and benefits of tofacitinib therapy proposed for the treatment of adults with moderate to severely active ulcerative colitis.

Before we begin, I would like to acknowledge that an additional errata to the FDA background document was issued within the last 24 hours. In case participants were not able to view it in advance of today's meeting, I will now read the contents into the record.

"On page 9 of the background document, it erroneously states that no deaths occurred in the induction trials. The accurate information is that 1 of the 5 deaths reported in the UC development program occurred during the induction period. Additional details of deaths occurring within the program are accurately described on page 65 of the FDA background document."

I will now give a brief introduction to the matter being discussed today. As many of you know, ulcerative colitis is a chronic inflammatory disease affecting the colon, and currently there is

no cure. More than 900,000 U.S. adults are affected. Patients experience recurrent flares of abdominal pain, bloody diarrhea, which may be associated with various extra intestinal manifestations. Available treatments are aimed at controlling symptoms, reducing complications, avoiding the need for surgery, and reducing the long-term risks of colon cancer.

The application being discussed today is a supplemental NDA submitted by Prism, an affiliate of Pfizer, for the use of tofacitinib in patients with moderate to severely active ulcerative colitis who have had inadequate response, loss of response, or intolerance to corticosteroids, azathioprine, 6-mercaptopurine, or TNF-blocker therapy. Tofacitinib is an inhibitor of Janus kinase enzymes and a potent immunosuppressant. The drug is an orally administered small molecule.

With the exception of oral corticosteroids intended for acute management of flares, all of the currently approved treatments for patients with moderate to severe UC are listed on this slide.

While other treatments such as thiopurines are available, they are used off label in this indication. Despite advances in this area, there remains a need for novel therapies for this condition.

It is notable that all of these approved therapies intended for chronic management of moderate to severe UC are therapeutic biologics and are administered parenterally. If approved, tofacitinib will represent the first approval of an orally administered drug intended for the chronic treatment of patients with moderate to severe UC.

I stress this point because this difference in mode of administration may be seen as a major benefit to patients, reducing the burden of traveling to infusion sites or working with specialty pharmacies to obtain injections that require refrigeration, training to use, sharps disposal, and potentially discomfort with administration. Further, small molecules are generally not associated with the risk of immunogenecity, which can result in acute or

delayed hypersensitivity reactions.

It is anticipated that if approved, uptake of tofacitinib into the market would be high. While the applicant's proposed indication is for the use of tofacitinib as a second-line therapy, the proposed indication does not limit its use to those who have failed TNF blockers. It is important that GI providers are aware of the risks, benefits, and uncertainties identified within this development program in order to make an informed recommendation to their patients regarding a choice of therapy.

The goals of today's advisory committee discussion are to discuss the proposed dosing regimen, risks identified, and areas of uncertainty based on the available safety database and to understand the strengths and limitations of the efficacy data with a particular focus on the treatment of those patients who have previously failed TNF blocker therapy and those who failed to demonstrate a response to tofacitinib therapy within the first 8 weeks of treatment.

Tofacitinib has been evaluated across multiple indications as shown here. The initial U.S. approval was for the treatment of adults with moderate to severely active rheumatoid arthritis who have had inadequate response or intolerance to methotrexate. The approved dose was 5 milligrams twice daily, and later an 11-milligram, once daily, extended-release formulation was developed.

The drug was evaluated for the treatment of chronic plaque psoriasis, but the application received a complete response from the agency and was later withdrawn by the applicant. Most recently, the supplemental application for the treatment of psoriatic arthritis was approved this past December. The division notes that across the approved indications, only a 5-milligram, twice daily dose was approved. This supplemental application proposes the use of a higher 10-milligram BID dose not currently approved for any other inflammatory condition.

In general, the following are important considerations in IBD drug development. These too

provide an opportunity to determine several important pieces of information. Adequate dose finding to determine an optimal dose or doses for confirmation in phase 3 is crucial. The other piece to understand is the time to onset of action and expected magnitude of clinical benefit.

While the agency acknowledges the paradigm of induction versus maintenance that has been historically utilized in IBD drug development programs is somewhat artificial, it is necessary for the chosen design of a program, be it induction and maintenance versus a treat-through design, to account for the following: first, the minimum time to expected initial clinical response or how rapidly patients start to note some improvement; second, the time to achieve remission in a substantial portion of patients, which will inform the appropriate time point for evaluation of the induction of remission in phase 3; and third, the need to demonstrate the durability of treatment benefit over time in this chronic disease.

The study design should be selected to

generate sufficient controlled clinical data to provide substantial evidence of efficacy for the proposed dosing regimens. Historically, sponsors have conducted dose finding across a broad range of doses for short term, as was done in this program, but at times neglected the need for dose finding for the long term or maintenance dose. When safety concerns do arise, this can result in difficulty determining the lowest effective or safest effective dose.

In general, a phase 3 program should be designed to confirm the efficacy of a selected dose or doses and should include a broad patient population so that differences in efficacy or safety can be reasonably assessed across different subpopulations of interest. Limitations in the design of this tofacitinib development program as they pertain to understanding the time required to induce remission and the adequacy of the data to support alternate dosing regimens across different subgroups will be a major focus of today's discussions.

The applicant proposes the following dosing regimens. The basic recommended dosing is 10 milligrams BID for 8 weeks followed by 5 milligrams BID long term. The division agrees with the applicant that the efficacy was demonstrated for the study population overall based on the specified primary and key secondary endpoints.

The proposals to extend dosing with 10 milligrams BID beyond 8 weeks apply to two subpopulations, those who may not have achieved adequate therapeutic benefit by week 8 and those with refractory disease, which the sponsor defines as prior TNF blocker failure. As you will hear today, several safety signals appear to be dose dependent, occurring in greater frequency among patients treated with the higher 10-milligram dose long term compared with the lower 5-milligram dose.

The analyses you will see presented today regarding efficacy of these alternate dosing regimens are all considered hypothesis generating in nature. An assessment of these subpopulations

and related alternate dosing regimens was not adequately accounted for in the overall study design and the prespecified analysis plan. With these considerations in mind, the division is requesting the input of the advisory committee regarding the adequacy of the data in support of these proposals for extending any use of 10 milligrams BID past the initial 8 weeks.

As you hear the presentations this morning, please keep the following questions for discussion in mind. The afternoon's discussion session will focus on the following topics.

First, in regard to patients who had inadequate therapeutic benefit by week 8, the applicant proposes that these patients may continue induction therapy with the 10 milligrams BID for an additional 8 weeks or 16 weeks in total.

We are interested in having discussion regarding the adequacy of the efficacy and safety data to support this recommendation. A voting question will be posed to the committee regarding whether or not you recommend inclusion of this

dosing regimen in the product label.

In follow-up, we are interested in the committee's input as to how a clinician in practice might distinguish among patients who are not doing well at the end of 8 weeks, which should continue therapy for another 8 weeks or more, and which should be permanently discontinued and switched to an alternate therapeutic option.

Second, pertaining to patients with a history of inadequate response, loss of response, or intolerance to prior TNF blocker therapy, we are interested in your input regarding the adequacy of the safety and efficacy data to potentially support the long-term use of the 10-milligram dose. Voting questions will be posed to the committee to address, 1) if you recommend including this proposed long-term use of 10 milligrams BID for this subpopulation in the product label; and 2) if you recommend that the applicant be required to conduct an additional trial to better elucidate the efficacy of the 10-milligram BID long-term dose in this population.

Further, we have the following nonvoting questions, which we hope to have discussion on; specifically, whether the committee members believe that additional postmarketing evaluation of safety is warranted, and if so, which mechanisms should be considered. In addition, we are interested in the input regarding the following aspects of the proposed pediatric development program.

First, if there are unique characteristics of the pediatric UC population that the agency should consider when planning the tofacitinib development program with the applicant, and specifically what is known about the ontogeny of the immune system in younger pediatric patients and how this may interact with the a drug such as tofacitinib.

Second, based on the committee's conclusions regarding the acceptability of the 10-milligram dose for any long-term use in adults, we are interested in how that may affect the appropriate exposures to target in the pediatric development program.

Lastly, based on committee members' understanding of how the safety profile of tofacitinib compares with other available agents, whether the agency should consider imposing a limitation on the population that could enroll in the pediatric UC trials and whether or not more stringent limitations of use should be considered for pediatric patients overall such as reserving tofacitinib only for those pediatric patients who have failed other advance therapies, meaning specifically approved biologics.

So again, I think you for taking the time to be here today, and I will now turn the podium over to the presenters from Pfizer.

DR. RAUFMAN: Before we proceed, we have one of our panel members on the phone.

Dr. Assis, could you please introduce yourself?

DR. ASSIS: Yes. Hi. Dr. Assis, assistant professor of medicine in GI and hepatology at Yale University School of Medicine.

DR. RAUFMAN: Thank you.

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

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

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

presentations.

Applicant Presentation - Lou Ferrara

MR. FERRARA: Good morning, Mr. Chairman, members of the advisory committee, and members of the FDA. Thank you for this opportunity to present the data supporting the approval of tofacitinib, a new treatment option for patients with moderate to severe ulcerative colitis.

My name is Lou Ferrara. I'm the global and U.S. regulatory lead for tofacitinib for ulcerative colitis. The only therapies currently approved as monotherapy for moderate to severe UC are biologic drugs. There are only two mechanisms of action for these biologics, TNF blockers and an anti-integrin agent. Despite these therapies, many patients either fail to respond initially or lose efficacy with time.

During the course of today's presentation, we will show that JAK inhibition by tofacitinib provides a new treatment option for ulcerative colitis. The data we present today will show that tofacitinib induces and maintains steroid-free

remission in UC patients. Efficacy has been demonstrated in both TNF naive and TNF experienced patients. The highest unmet need is for new treatment options for the TNF experienced population.

There are a number of important properties of tofacitinib. Tofacitinib is an oral, small molecule inhibitor of the Janus family of kinases. Dosed twice daily, direct inhibition by tofacitinib is partial at the proposed doses and is readily reversible if needed. Human genetics implicate JAK-dependent cytokines in UC pathogenesis.

The immune effects of tofacitinib have been extensively studied, and the safety of tofacitinib is well characterized. These properties of tofacitinib lead to the following therapeutic features: low risk of antidrug antibodies; direct and reversible JAK inhibition that modulates important pathways that drive UC pathogenesis; and a well characterized and manageable safety profile.

Tofacitinib has been studied clinically for over 16 years in over 12,000 patients, which has

led to a number of approvals. Xeljanz has been approved for the treatment of rheumatoid arthritis since 2012 and recently approved in December 2017 for the treatment of psoriatic arthritis. There is over 100,000 patient-years of postmarketing exposure to Xeljanz. The UC supplemental NDA application was submitted in May of last year and is the subject of this meeting.

The approval of tofacitinib monotherapy for the treatment of moderately to severely active UC patients is supported by the following. There is a significant medical need for alternative UC treatments with new mechanisms of action. Tofacitinib provides clinically meaningful benefit for both induction and maintenance. Many patients achieve induction treatment targets and durable steroid-free benefit and maintenance. This benefit is comparable between TNF naive and prior TNF treatment failure patients.

The safety profile of tofacitinib in UC patients is well characterized, manageable, and qualitatively similar between doses. We have a

targeted risk management plan to address risks of UC patients that builds on the current comprehensive risk management plan for Xeljanz. Based upon the tofacitinib UC data, we have proposed the following indication and dosing.

The proposed indication is for the treatment of adult patients with moderately to severely active ulcerative colitis who have failed the prior therapy. The recommended dosing is as shown, and we use the map on the next slide throughout our presentation when presenting the supporting data for these dosing posologies.

The top of the map shows the primary posology for the moderate to severe UC patient. They would receive 10 milligrams induction for 8 weeks followed by 5 milligrams maintenance. There are two options in the posology related to subpopulations of moderate to severe UC patients, the TNF treatment failure subpopulation and the extended induction subpopulation, which we will cover in the course of our presentation.

For the treatment failure subpopulation, the

proposed posology is for induction and maintenance with 10 milligrams, which is a dose of 10 milligrams continuously. For the extended induction subpopulation, this patient subset is defined by treatment response. For this posology, the recommendation is for the moderate to severe patients to extend induction for up to 16 weeks if they did not achieve a good clinical response by week 8.

During our presentation, we will describe the efficacy, safety, and risk-benefit data that support approval for these dosing recommendations. We will also describe our risk management plan to ensure safe and proper use of the 10-milligram BID dose for UC patients.

I now have the privilege of introducing Dr. William Sandborn. Dr. Sandborn is chief, Division of Gastroenterology, and director, Inflammatory Bowel Disease Center, University of California San Diego, who will describe the burden of disease of UC and unmet needs. Before Dr. Sandborn begins his presentation, I would also

like to acknowledge the additional experts in attendance on the sponsor's behalf, Dr. Sands, Schein, and Schooley.

I now turn the presentation over to Dr. Sandborn.

Applicant Presentation - William Sandborn

DR. SANDBORN: Thank you, Mr. Ferrara.

Mr. Chairman, members of the advisory committee, and members of the FDA, I'm pleased to be here today to present a physician's perspective on the unmet need in ulcerative colitis. I have been compensated by the sponsor to be here today, but I have no financial interest in the outcome of this meeting. However, I do have a personal and professional interest, as I've been a practicing gastroenterologist for over 25 years, specializing in the treatment of patients with inflammatory bowel disease.

In addition, I have served as the primary investigator for the global trials for all of the approved advanced agents for ulcerative colitis, as well as for the tofacitinib global trials.

Ulcerative colitis is a chronic inflammatory bowel disease with an unpredictable course. It's idiopathic, it's not curable, and affects the colon. The hallmark symptoms include diarrhea with 10, 15, even 20 stools per day in the moderate to severe patient population, rectal bleeding, fecal urgency, tenesmus, profound fatigue, and abdominal pain. It has an early age of onset with half of patients before the age of 30 and a rising incidence and prevalence, and it affects about 900,000 Americans.

Ulcerative colitis can cause significant disruption to patients' everyday lives. There are a number of effects. I'm going to pick a few of them here. Seventy-nine percent of patients believe that ulcerative colitis prevented them from leading a normal life, 74 percent of patients reported feeling depressed as a result of having ulcerative colitis, and 84 percent of patients worry about the long-term effects of their disease. All of these effects roll up to a loss of autonomy for the patient.

There are significant consequences from the disease burden over time. One of those consequences is a rising risk of colorectal cancer. Beginning at approximately 10 years from the time of diagnosis, you can see a progressive rise up to a risk of 18 percent at 30 years from diagnosis or overall about a 2.4-fold increased risk relative to controls. This risk is increased with the anatomic extent of disease and the severity of inflammation, so patients who fail to achieve response and remission will have a higher risk of colorectal cancer. For that reason, colorectal cancer associated with ulcerative colitis is a modifiable risk.

Another consequence of the disease burden is the need for surgery and colectomy. You can see on the graph at the top that there's been some decrease in the colectomy rates over time, but still in recent cohorts you have an absolute risk of colectomy of 9 percent just 9 years after diagnosis, and it eventually rises up to greater than 20 percent.

Ulcerative colitis surgery is associated with morbidity, mortality, and a decreased quality of life. Pouchitis can occur in up to 50 percent of patients, and some patients will have chronic pouchitis. We often don't stop to think about the mortality associated with colectomy for ulcerative colitis, but when you get into the details, it can be in the range of 2 percent and in the high single digits in patients who are operated in low-volume surgical centers and in patients who are hospitalized for severe colitis-failing steroids and biologics.

The median stool frequency after colectomy with a ileal anal pouch, it's about 7 stools per day, meaning that half of patients will have more frequent stools than that. So the idea that you could cure ulcerative colitis really seems misguided. Surgery is not a cure for this condition.

It's worthwhile as we begin the day to think about the approach and the goals to treatment in patients with ulcerative colitis. As was mentioned

previously, we have two phases of treatment. One is the induction phase, and then the second is the maintenance phase. For induction, a very specific measure of induction is the induction of remission over some period of 8 to 10 weeks. However, in clinical practice, we don't focus so much on inducing remission during the induction phase, but rather getting a grip on the patient's symptoms and seeing a rapid improvement in clinical response.

As times has gone on, there's more and more thought that the induction phase would run out to 12 to 16 weeks before you would back away from concluding that an agent is failing, and then the maintenance phase begins out at that 12- to 16-week mark. And during the maintenance phase, you really want to see consolidation of the benefits with conversion of patients who initially responded but did not remit into remitters, for the early remitters to retain remission, and the discontinuation of steroids and mucosal healing.

It's worth pointing out -- and you'll hear this again from the sponsor in a few

minutes -- that in the tofacitinib development program, the patients were required during the maintenance phase of the trial to taper steroids and discontinue them. If they were unable to do that, they had to exit the trial and their values would be carried forward as failures.

This is the only trial that I'm aware of that has done this in ulcerative colitis. Most other studies would allow recycling of steroids if patients were unable to wean. So in this trial when you see the steroid-free remission rates at the end of the year, that's the same as the remission rates, and that's really unique data.

Let's think about the treatment options for ulcerative colitis. About half of patients have mild to moderate ulcerative colitis. They respond to topical therapies and oral mesalamine and are easy to treat. Those are the lucky patients. That's who we're not going to talk about today. What we're going to talk about is the moderate to severe patients that have failed those first-line therapies, and those patients have few treatment

options. They roll up into steroids, immune suppressives, specifically 6-mercaptopurine and azathioprine, and then biologic drugs.

Let's talk about the steroids and immune suppressives first. It's ironic actually that we're discussing tofacitinib today and requiring that patients go through unapproved therapy with thiopurines, which have a significant amount of toxicity. With steroids, it's now well documented that there's an unequivocal increase in mortality if you take prednisone more than 20 milligrams a day for more than 60 days. I think all of us recognize that the most dangerous drug that we use in clinical practice is prednisone, and there are a variety of other side effects from steroids that you're well acquainted with.

What about the thiopurines? If you look at the Cochran reviews on efficacy, there's no evidence of efficacy for thiopurines for induction therapy, and the evidence of efficacy as maintenance therapy is very modest, perhaps in the range of 10 percent. It's based on small numbers.

Most of the individual trials are negative, and the evidence base is not such that it would allow approval of the drug if it were to come before a committee like this. So the efficacy for thiopurines is modest.

What about the safety issues? It's very well described that there's a 4-fold increased risk of non-melanoma skin cancer, a 4-fold increased risk of non-Hodgkin's lymphoma. There's a risk of hepatosplenic T-cell lymphoma, which is further increased if thiopurines are combined with TNF blockers.

There's a significant risk of bone marrow depression, which is much greater than what's described with tofacitinib as the doses that were studied. You can see serious and opportunistic infections and you see frequently viral infections. So we see a lot of herpes zoster with azathioprine and mercaptopurine, at least in the range of what was described at the higher dose of tofacitinib, so for that therapy class, minimal efficacy and a significant amount of adverse events.

Then we go on to the biologics. We have three anti-TNF drugs. They're clearly effective, but you recognize the side effects of opportunistic infections, especially granuloma infections, tuberculosis, and fungal infections, serious infections, demyleination, and other side effects. It's also now well described that there's an independent risk of non-Hodgkin's lymphoma with TNF-blocker monotherapy, and you add to that risk if you combine TNF blockers with thiopurines in terms of the overall risk of non-Hodgkin's lymphoma.

Vedolizumab has quite a good safety profile, but as we'll discuss in a moment, its efficacy in anti-TNF failure purpose is somewhat limited. So there's a real need for additional mechanisms of action.

What are the limitations of the approved biologic therapies? We see primary failure with first-line anti-TNF therapy in numbers as many as 50 percent of patients and 53 percent of patients treated with vedolizumab. So what does that mean?

It means that patients, not only did they not have a remission, they didn't have any clinical response. So 50 percent of the patients saw absolutely nothing with the currently available therapies. What should we do with those patients in our clinical practice?

Among the patients who respond, you'll see secondary loss of response in up to 37 percent or so of patients over the next 1 to 2 years. How does this secondary loss of response occur? One way that it happens is immunogenecity. These are protein-based therapies that are administered intermittently, and we know that the cumulative rates of antidrug antibody formation and abrogation of efficacy, as well as side effects, can occur during maintenance therapy with biologics. We also know that once you've failed one biologic, if you switch to another biologic, the absolute level of efficacy is reduced.

Professional societies have now recommended the use of therapeutic drug monitoring to identify patients who have high clearance of the biologic

drug due to target-mediated clearance and then due to the formation of antidrug antibodies. Particularly as you fail one biologic and start going into others, I think the clinicians on the panel will recognize that you start to really ramp up therapy. So pretty quickly you're using off-label dosing, intensive dosing of the biologic, very often in combination with azathioprine or 6-mercaptopurine and very often in combination with prednisone, 40 to 60 milligrams per day.

So as we think about the adverse event profile with monotherapy with tofacitinib 10 milligrams, you have to think through what's going to happen to these anti-TNF refractory patients. If they don't have tofacitinib as an option, they're very often going to be getting double or triple therapy with drugs that have a lot of side effects.

Let's look a little bit in detail at the currently available drugs in the TNF-blocker failure population. If you recall, infliximab was studied in anti-TNF naive patients. It's never

been studied in anti-TNF failure patients. It's not indicated in that patient population.

Adalimumab was studied in a mixed population of naive and failure patients, however, the clinical benefit in the failure population was low single digits, very low. So ultimately the drug was only approved for use in anti-TNF naive patients, so it's not approved for failure patients. Golimumab was only studied in anti-TNF naive patients. So none of the available TNF blockers are approved for use in anti-TNF failure populations.

Vedolizumab was studied in a mixed population. About half the patients were anti-TNF failure and half were anti-TNF naive. When you look at the details in the subgroup of patients who were anti-TNF failure during the induction phase, there was not statistical evidence of benefit for induction in the anti-TNF failure population. In the maintenance phase, there was evidence of benefit in the anti-TNF failure population, so the drug was ultimately approved for both the anti-TNF

and the anti-TNF failure patients with ulcerative colitis despite the fact that there wasn't statistical evidence of benefit during induction.

The other thing to say with vedolizumab, the induction trials were 6 weeks in duration but the ultimate label allowed patients to stay on the therapy for up to 14 weeks before concluding that there wasn't benefit. That was based on data that's very similar to what you'll see today with tofacitinib. So the last drug approved for ulcerative colitis allowed for an additional 8 weeks of therapy in nonresponding patients based on a very similar analysis to what you'll be looking at.

So this leads us to a therapeutic void in ulcerative colitis. There are only two approved mechanisms of action for advanced therapies. The current biologic therapies are parenteral, either intravenous or subcutaneous. They're limited by loss of efficacy and by the adverse events and the context of the anti-TNF drugs. Anti-integrin therapy has a relatively show onset of action, and

dose flexibility is important, but the way the drugs are labeled is lacking.

So they have just a single dose that's approved, and the dose intensification that's done in clinical practice according to professional society guidelines ends up being done off label because the broader dosing regimens were not approved.

So how could tofacitinib help address these unmet needs? It has a rapid onset of action. The effect is durable. You see durable response, remission, and steroid-free remission. And again, I can't emphasize enough the fact that the remission rates and the steroid-free remission rates are virtually identical, and that's unique to this clinical trial program. You see efficacy across patient populations, including the difficult to treat TNF-blocker failure patient population for which very little else is approved.

The drug can be orally administered. We heard during the introduction how important that would be, and couldn't agree with that more that

this is an important factor for both patients and prescribers. And ultimately, the safety profile I believe is manageable. Gastroenterologists are very used to seeing non-melanoma skin cancer and herpes zoster in the setting of thiopurine and steroid therapy. We are used to having a rare but real event rate of non-Hodgkin's lymphoma from thiopurines and TNF blockers. We're used to seeing serious infections from steroids, thiopurines, and TNF blockers, and I think that our specialty will be able to recognize and advise patients appropriately and manage these complications when they occur. Thank you for your attention.

I'd next like to introduce Dr. Eric Maller, who will present the efficacy data.

Applicant Presentation - Eric Maller

DR. MALLER: Thank you, Dr. Sandborn.

My name is Dr. Eric Maller from Pfizer clinical development, and I will be taking you through a review of the overall tofacitinib UC development program and summarizing the key efficacy results that support Pfizer's proposed

label dosing. We will first review the design and results of the phase 2 study that supported the phase 3 induction dose selection. Next, we'll review the design of the pivotal phase 3 program, its efficacy endpoints, and then the phase 3 induction and maintenance results with an additional focus on the subgroups by prior TNF treatment failure. Lastly, we will discuss the special case of extending induction therapy with tofacitinib 10 milligrams BID up to 16 weeks total for initial 8-week induction nonresponders.

These are the three components and populations of the proposed dosing posology that Mr. Ferrara showed you for tofacitinib treatment of UC, and we will present the efficacy data that supports each of these proposed dosing recommendations.

The phase 2 study evaluated doses ranging from 0.5 milligrams to 15 milligrams over 8 weeks in patients with moderate to severe UC who were not treatment naive. The results for the primary endpoint of clinical response on the left show a

dose response with the 10-milligram and 15-milligram doses showing the greatest effect. The results for clinical remission on the right similarly show greatest effect at 10 milligrams, approximately 38 percentage points difference from placebo that was observed for clinical remission without additional effect observed for the 15-milligram dose.

We took the data observed in this phase 2 study and modeled the results, which prompted us to initially choose the 10- and 15-milligram doses to bring forward to phase 3. Subsequent further modeling of the completed phase 3 induction results confirm that a 5-milligram dose would have achieved 30 to 40 percent lower efficacy for remission than the 10-milligram dose did that was used for induction in phase 3.

The phase 3 UC program consisted of 2 replicate 8-week double-blind induction studies that evaluated 10 milligrams and placebo in a 4 to 1 ratio. The initially selected 15-milligram dose was removed shortly after the program began

enrolling. Clinical responders at 8 weeks entered a single 52-week, double-blind maintenance study and were rerandomized in equal proportions to 10 milligrams, 5 milligram, or placebo.

There was a single open-label, long-term extension study. Patients completing maintenance and remission could enter this LTE and receive 5 milligrams. All others entering the LTE study received 10 milligrams and included nonresponders to 8 weeks of induction therapy, which we will discuss in detail later, maintenance treatment failures, and maintenance completers who completed this study but were not in remission. We will discuss the individual components of the phase 3 program and their results separately beginning with induction.

Entry into the tofacitinib phase 3 program consisted of two identically designed, randomized, double-blind induction, studies shown here at induction 1 and 2, evaluating 10 milligrams versus placebo in a 4 to 1 ratio. Key entry criteria for the phase 3 program included moderately to severely

active UC, which required a total Mayo score of at least 6 out of a maximal score of 12, including requiring a rectal bleeding subscore of at least 1 and an endoscopic subscore of at least 2, and with a history of prior failure of at least one of the agents listed on this slide.

Patients could enter and remain throughout the study on stable doses of 5 aminosalicylates or equivalent containing compounds or oral corticosteroids at the maximal doses as shown. Patients during this study were prohibited from taking immunomodulators or biologic agents for UC treatment.

There was also a mandatory taper of any corticosteroids once patients exited the induction studies to either the maintenance of long-term extension study. Most patients were then free of steroid therapy by week 7 of the maintenance or LTE study and were therefore being treated with tofacitinib maintenance monotherapy except for 5 aminosalicylates for the majority of the maintenance and LTE studies.

We now turn to the 8-week controlled induction study results. The pooled disposition of patients in the replicate phase 3 induction studies is shown here. Of note are the low overall discontinuation rates with more than 90 percent of patients in both groups completing induction. The tofacitinib and placebo groups across the two induction studies also had similar baseline characteristics.

The patient population had chronic UC with median disease duration across both induction studies of more than 6 years with the majority of patients having extensive disease, including pancolitis. For both treatment groups, mean total Mayo score was 9 out of a possible maximum of 12 and more than 50 percent had failed prior TNF-blocker treatment. Almost half the patients were taking corticosteroids at baseline at the similar mean doses shown.

Summarized here are the primary and key secondary endpoints and two additional important secondary endpoints for the 8-week induction and

52-week maintenance studies. Two items are worth noting that distinguished endpoint assessment in this phase 3 development program from other programs. First, the induction and maintenance primary endpoints that included remission required that the Mayo rectal bleeding subscore was equal to zero, a more rigorous definition for remission than used in previous trials of currently approved therapies for UC where rectal bleeding subscore for remission could be zero or 1.

This endpoint where rectal bleeding subscore equals zero or 1 we called clinical remission to distinguish it from our primary endpoint of remission. Second, the tofacitinib UC program was the first UC pivotal phase 3 program to use central endoscopic reading to assess both eligibility and study endpoints in order to mitigate potential variability especially in the placebo rate due to local reading at each study site. This is important when comparing tofacitinib results to rates for active and placebo therapy from the literature for other approved agents, all of which

were obtained using local reading endoscopy.

Using this more rigorous definition for remission and central reading for remission, we also evaluated the highly stringent and clinically relevant endpoint of sustained steroid-free remission among baseline remitters which involved sustained maintenance of remission, and that is remission present at both weeks 24 and 52 among patients in remission at baseline, as well as being steroid free at both weeks 24 and 52, effectively achieving monotherapy treatment for UC.

Note that this key maintenance alpha-controlled secondary endpoint of sustained steroid-free remission among baseline remitters satisfies and goes beyond FDA's requirement for measuring maintenance of remission only among those in remission at baseline. The prespecified criteria defining clinical response, the entry gateway from induction to enter maintenance, are outlined here as well.

For this analysis of the induction results, the gray bars represent placebo and the orange bars

tofacitinib 10 milligrams. The results illustrate that the induction efficacy for tofacitinib 10 milligrams versus placebo across both the primary endpoint of remission and key secondary endpoint of endoscope mucosal healing was statistically significant and consistent across both replicate induction studies. The same can be said for clinical response, the prespecified secondary endpoint that served as the minimum requirement for entry from induction into maintenance.

Additionally, significant improvements in patient reported quality-of-life outcomes measured by the SF36 and IBDQ instruments summarized in your briefing document were consistent with the results from the clinical and endoscopic endpoint results.

We looked at prespecified TNF treatment failure subgroups as well. This analysis shows the induction results for 10 milligrams versus placebo for the primary endpoint of remission and the key secondary endpoint of endoscopic mucosal healing in patients with and without prior TNF treatment

failure. The placebo corrected results for both endpoints are quite similar regardless of prior TNF treatment failure status, which is a unique finding compared to all currently approved therapies for UC.

We will now discuss the efficacy data that support both the recommendation for 5 milligrams maintenance and also consideration of 10 milligrams for those specifically with prior TNF treatment failure. Although the primary induction endpoint was remission, patients achieving at least clinical response after completing the 8-week induction studies, as illustrated by their shorter open blue arrows, were eligible to enter the blinded 52-week maintenance study and were rerandomized to placebo 5 milligrams or 10 milligrams in equal proportions.

Although inducing and maintaining remission is the ultimate goal of UC therapy, Dr. Sandborn emphasized that the clinical response is also a highly clinically meaningful induction and maintenance goal for a patient population with moderately to severely active UC, all of whom had

failed or been intolerant to at least one prior therapy, and in this population more than half of which had failed or been intolerant to at least one prior TNF treatment.

Shown here is the disposition flow chart for patients in the maintenance study. The analyses shown in subsequent slides for maintenance treatment are from the mFAS or modified full analysis set maintenance study population of 523 patients indicated in the top-most box; that is, only those who had taken tofacitinib during induction and not including the 70 patients who took placebo and showed clinical response after 8 weeks of induction and so entered the maintenance study.

This modified population represents the real-world treatment situation of those receiving active induction, achieving clinical response by week 8, and subsequent active therapy and maintenance. Note that the differences in discontinuation rates were predominantly driven by the different rates of insufficient clinical

response among the dose groups with the highest rate in the placebo group. There were low and similar levels less than 5 percent across all three groups for discontinuation due to adverse events.

Shown here with placebo in the gray bars, 5 milligrams in the blue bars, and 10 milligrams in the orange bars are results for the primary and key secondary endpoints for the overall maintenance study modified FAS population. There is significant and consistent efficacy for both 5 milligrams and 10 milligrams versus placebo at week 52 across all endpoints.

This significant efficacy is present for both doses, even for the highly stringent key secondary endpoint of sustained steroid-free remission among baseline remitters shown on the right. Additionally, as for induction, these results for the clinical and endoscopic endpoints in maintenance were also supported by consistent results for patient reported quality-of-life outcomes as summarized in your briefing document.

While 10 milligrams shows numerically

greater benefit compared to 5 milligrams in the overall maintenance study population, we were particularly interested in examining whether the overall difference between 10 milligrams and 5 milligrams in maintenance was driven by key subgroups.

Next, we will return to the prespecified analysis of the maintenance treatment effects of 5 milligrams and 10 milligrams in prior TNF treatment failure subgroups. We focused on and prespecified this particular subgroup analysis given the recognized difficulty in treating the population with prior TNF treatment failure and the very limited effective treatment options available to this population using currently approved therapies.

Shown here are the 52-week results for the subgroup of patients without prior TNF treatment failure. The results are again consistent across all three primary and key secondary endpoints. The difference between the proportions for 10 versus 5 milligrams is modest for remission in this

subgroup with 41 percent achieving remission with 5 milligrams and 45 percent for 10 milligrams, though the difference between doses is larger for the two key secondary endpoints ranging from a 20 to 25 percent relative increase from the 5- to the 10-milligram dose.

Shown here in comparison are the results for the subgroup with primary TNF treatment failure. The results are again consistent across all endpoints, though with larger relative increases between the 10-milligram versus the 5-milligram doses than those seen in patients without prior TNF treatment failure in the prior slide ranging here from 70 to 75 percent for the remission-based endpoints and nearly 40 percent for endoscopic mucosal healing.

Almost 36 percent of patients with prior TNF treatment failure achieved remission with 10 milligrams and almost 40 percent of patients achieved endoscopic mucosal healing or sustained steroid-free remission among baseline remitters. For remission, the difference between 5 milligrams

and placebo is much smaller than in the prior population without TNF treatment failure, and the difference between 10 milligrams versus 5 milligrams in TNF treatment failure patients is numerically greater than the difference between 5 milligrams and placebo.

Although our studies were not designed or powered for formal comparison between 10 and 5 milligrams in subgroups, these results are again consistent across all three primary and key secondary endpoints and support the interpretation that 10 milligrams maintenance provides clinically meaningful additional benefit versus 5 milligrams in prior TNF treatment failures. These data support the proposed dosing recommendations that give providers dosing flexibility and provides for consideration of 10 milligrams as a maintenance dose for these difficult to treat UC patients.

Now it is true that although the TNF subgroup analysis was prespecified, the pairwise comparison between 10 and 5 milligrams for either subgroup was not. However, the magnitude of the

difference between the 5- and 10-milligram doses is noteworthy. Therefore, there is value in examining the strength of this difference between 10 milligrams versus 5 milligrams across the subgroups by examining nominal statistical testing for the pairwise comparisons between doses.

Here we show for both prior TNF treatment failure subgroups in the modified full analysis set population the differences in proportions of patients achieving remission for 10 milligrams versus 5 milligrams. Shown on the left in the green bar is the difference in proportions for the 10-milligram versus 5-milligram doses for remission at week 52 in the subgroup with prior TNF treatment failure.

We see that the difference for remission between the two doses is 14.8 percentage points with a nominal p-value for this comparison of 0.04 by central reading. In contrast shown on the right in the yellow bar is the comparison of 10 versus 5 milligrams for remission for the subgroup without prior TNF treatment failure. The difference

between doses is smaller and quite modest at 4.3 percentage points with nominal p-value greater than 0.05.

The data show a more clinically meaningful treatment effect for the 10- milligram dose versus the 5-milligram dose in prior TNF treatment failures. These analyses again support the proposed recommendation for dosing flexibility in considering 10 milligrams for maintenance therapy in patients with prior TNF treatment failure.

We will now turn to examine the efficacy data for those patients who received extended induction therapy with tofacitinib 10 milligrams up to 16 weeks. The induction nonresponders are those patients of the original 905 patients taking tofacitinib 10 milligrams from the combined controlled replicate induction studies shown in the lower left who did not achieve clinical response after completing 8 weeks treatment.

These nonresponding patients were offered the opportunity to enroll directly into the open-label, long-term extension study as reflected

by the open purple arrows and receive an additional 8 weeks of treatment with tofacitinib 10 milligrams shown on the right. After a total of 16 weeks of induction treatment, if patients did not achieve clinical response, then they were required to discontinue from the program.

We will now focus specifically on the treatment results for the induction nonresponders who failed to achieve clinical response among the original tofacitinib 10-milligram induction patients and their course after they entered the long-term extension study. On the left are those patients who received an additional 8 weeks of 10 milligrams in the long-term extension for a total of 16 weeks of 10 milligrams and achieved clinical response after that 16 weeks. These delayed responding patients comprised 51 percent of the total 10-milligram induction nonresponders cohort.

Now, it is reasonable to ask whether this additional benefit evident in these delayed responders at week 8 of the LTE is limited to

clinical response or is it also demonstrable with other more rigorous endpoints and is it sustained over time and not just a short-term gain?

This slide shows the status at one year in the LTE of those delayed responders who took 16 weeks total of 10 milligrams to achieve their clinical response. On the left is a reminder of those delayed responding patients after 8 weeks in the LTE or 51 percent of the total 10-milligram induction nonresponders to the first 8 weeks just discussed.

Shown in the 4 bars to the right are the proportions of these same delayed responding patients at week 52 of the LTE. Overall, at one year in the LTE, 45 percent of the 10-milligram 16 week induction-delayed responders achieved remission, all of whom achieved steroid-free remission, 54 percent achieved mucosal healing, and 73 percent maintained the clinical response they achieved at week 8 of the long-term extension.

The results were also consistent regardless of prior TNF treatment failure across all four

endpoints. The results show a preponderance of clinical evidence supporting the additional clinically meaningful and durable efficacy associated with extended induction treatment.

Now let's return for a moment to those patients who did achieve clinical response with the first 8 weeks of 10-milligram induction therapy. Shown here in the solid orange bar are the pooled non-placebo corrected results of 57.6 percent clinical response among the 905 original patients who received 10 milligrams tofacitinib for 8 weeks in the replicate induction studies previously shown. If we now return to those 8-week induction nonresponders, the striped orange bar on the right again shows 51 percent of initial nonresponders who achieved clinical response after an additional 8 weeks of patient in the LTE.

Now if we express those delayed responding patients in striped orange as a percentage of the original total 905 patients in induction who took 10 milligrams of tofacitinib and combine these two patient populations with those who responded after

just 8 weeks in induction from the solid orange bar on the left, we see that these delayed-responding patients who showed response after a total of 16-weeks, 10-milligrams treatment, they add 16.5 percent to the overall combined response rate of close to 74 percent after 8 or 16 weeks induction as shown in the added solid orange and striped bars.

These data show that extending induction beyond 8 weeks for initial nonresponders provides clinically meaningful additional benefit for this delayed responding population achieving nearly 75 percent overall clinical response after 16 weeks of 10 milligrams among those 905 original patients first receiving 10-milligram induction therapy and support the proposed labeling for extending induction up to 16 weeks.

In summary, there is significant efficacy for tofacitinib 10 milligrams for 8 weeks induction overall and also regardless of prior TNF treatment failure. This equivalent efficacy in both TNF treatment failure subgroups is unique for induction

treatment among currently approved agents for treatment of UC. There is significant treatment effect with both 5 and 10 milligrams for 52-week maintenance therapy also regardless of prior TNF treatment failure.

Ten milligrams BID provides a consistently larger treatment effect than 5 milligrams across all endpoints, and the difference is most prominent and clinically meaningful among patients with prior TNF treatment failure. These findings support the proposed labeling to allow treatment flexibility for providers to consider 10 milligrams maintenance treatment for those patients with prior TNF treatment failure who as a group are the most difficult to treat patients and have the highest unmet treatment needs.

Finally, despite the significant 8-week induction efficacy previously demonstrated, regardless of prior TNF treatment failure, some delayed responding patients still failed to show adequate therapeutic benefit by week 8 of treatment. These 8-week initial induction

nonresponders may benefit from extended induction, achieving a total combined clinical response of close to 75 percent of patients receiving 8 or 16 weeks of 10 milligrams induction therapy. The benefit of extended induction is also present regardless of prior TNF treatment failure, is maintained longer term, and supports the proposed posology recommended in extended induction up to 16 weeks.

I would now like to introduce Dr. Chinyu Su, who will review the safety findings for the UC program.

Applicant Presentation - Chinyu Su

DR. SU: Good morning. I'm Dr. Chinyu Su from Pfizer development. This presentation will review tofacitinib safety data. For safety topics of special interest, I will also review data from our other indication that are consistent with the UC safety profile. This presentation will conclude with a safety summary for the three proposed dosing regimens listed here.

The UC safety data were analyzing three main

patient cohorts from the UC development program. First, the induction cohort describes data pooled across the three 8-week induction studies, and this group is particularly useful for examining short-term and routine safety measures. Second, the maintenance cohort includes the single phase 3 maintenance study, and this cohort looks at the safety profile over 52 weeks with placebo comparison.

Finally, the overall cohort evaluates safety across the entire UC development program and includes all treated patients from phase 2, phase 3, and the ongoing long-term extension study.

In this cohort, we assigned patients to either 5 milligrams or 10 milligrams based on the average daily dose of tofacitinib received, and we did that because patients may change dose from one study to next. As a reminder, there's no placebo comparison in this cohort, and to supplement the placebo-controlled maintenance data, we conducted analysis based on this average daily dose, also called the predominant dose. In this presentation,

we'll simply refer to them by the dose when describing treatment groups in this overall cohort. It's also important to keep in mind that because of the program design, over 80 percent of patients in this program were in the 10-milligram group.

UC safety data has been collected from 1,157 patients with 971 patients in the 10-milligram group. As of December 2016, 653 patients received tofacitinib for at least 12 months and 359 patients for at least 24 months. In total, the UC program has more than 1600 patient-years of exposure to 5 milligrams or 10 milligrams and up to 4.4 years of tofacitinib treatment.

The UC safety data are supported by extensive clinical trial patient experience from three other indications, mainly rheumatoid arthritis. All four indications totaled more than 12,000 patients with more than 34,000 patient-years of exposure. In addition, more than 100,000 patient-years of exposure have been accrued in the postmarketing setting. Importantly, a majority of our clinical trial experiences with more than

23,000 patient years came from the 10-milligram BID dose group.

For the general safety, this figure summarizes the proportions of patients with adverse events in the placebo-controlled UC trials. The gray bars are placebo. Orange and blue bars are tofacitinib. In both induction and maintenance cohorts, the proportions of patients with AEs were similar between placebo and tofacitinib. Most of the AEs were mild or moderate. Serious AEs were reportedly less than 10 percent of patients, and the AEs resulting in just a continuation less than 5 percent. These percentages were similar across treatment groups.

We carefully looked for special safety risks in the UC program, and these risks were included based on their mode of action over the drug and what we know from other indications. For select AEs of special interest, we used standardized review and external adjudication. When reviewing the safety events of the interest, we were focused on the overall cohort for long-term experiences,

and we will return to the 52-week maintenance cohort to inform dose response when there were sufficient numbers of events.

To further inform dose relationship and long-term use of 10 milligrams in UC patients, we will also describe the safety data from our extensive cross-indication experiences. This is appropriate because tofacitinib exposure is similar across indications. We also know from the literature, rates for rare safety events for a given drug are similar across autoimmune diseases, and therefore knowledge from other indications should be informative for UC.

To put our data into context, we identified a cohort of UC patients from a claims database that have similar characteristics of patients in the UC program, and the database we chose to use is a Truven MarketScan claims database, which has been used as a primary source of reference for many publications. This Truven cohort provides background rates for how comparable UC patients do in the real-world setting. While we recognize

limitations of this observational comparison cohort, it serves as an important contextual tool for us.

Starting with serious infections, this figure shows serious infections in the UC program. Incidence rates are along the X-axis and each shaded dot representing the point estimate with the horizontal lines showing the confidence interval. In the overall cohort, the incidence rate for serious infections was 1.87 per 100 patient-years. This rate is just within the range of serious infections reported for TNF blockers for UC patients in the Truven cohort. In UC, other than those events listed here, most serious infections were reported in only one patient each. No serious infections resulted in death.

Now, what about the RA experience? In RA, there was a dose relationship for serious infections. The most common serious infection was pneumonia as is typically observed in the RA patients. Most cases resolved with treatment. Less than 5 percent of cases resulted in death with

pneumonia being the most common infection leading to death. When compared against other RA treatments, the rates for serious infections were within the range of those reported for biologics in published trials.

One specific infection we've been following is herpes zoster. Herpes zoster is a known risk associated with tofacitinib treatment, and the findings we observed in UC were consistent with other indications. This slides shows the incidence rate of herpes zoster in UC in the same layout as shown earlier. In the overall cohort, the rate was 3.8 per 100 patient-years, which is higher than that observed in UC patients taking TNF blockers in Truven.

In the placebo-controlled maintenance study, we observed a dose relationship in the rate of herpes zoster. Most cases of herpes zoster in UC involved one to two adjacent dermatomes. The vast majority of events were mild or moderate and not reported as serious AEs. Many of these patients discontinued because protocols required

discontinuation for serious infections. More than 90 percent of patients were able to continue tofacitinib without permanent discontinuation.

Similar to what we saw in UC, in the RA program, a dose relationship was observed for herpes zoster. The cohort characteristics of the herpes zoster cases in RA are similar to that observed in UC. And when we look at the incidence rates at 6-month intervals, rates were stable, suggesting no increased interval rates of herpes zoster over time.

In the UC program, there were 4 known herpes zoster opportunistic infections, and this included one case each of pulmonary cryptococcus, pulmonary histoplasmosis, CMV hepatitis, and CMV colitis. The rate of known herpes zoster opportunistic infections in UC is within the range reported in rheumatoid arthritis.

Switching to malignancies, the rate of overall malignancies in UC was 0.74 per 100 patient-years, which is within the range observed for TNF blockers in Truven. Note this data were

updated from the briefing document to include all cases occurring before the data cutoff even if adjudication was not completed in time.

There were 15 patients with 12 malignancy types excluding non-melanoma skin cancer in the UC program. This included 2 colon cancers and 1 lymphoma. Mostly there was one patient for each cancer type. Four of these patients had metastatic disease at diagnosis, 4 resulted in death, 6 malignancies were reported within the first year of tofacitinib treatment, and consistent with a refractory UC population, most patients had received prior treatment with azathioprine or 6-MP and/or TNF blockers; 14 malignancies reported are in patients in the 10-milligram group and 1 in the 5-milligram group.

There have been two additional malignancies reported recently, one in breast cancer and one in B-cell lymphoma not associated with EBV. These two new cases were both in the 5-milligram group making a total of 17 patients with malignancies, 14 in the 10-milligram and 3 in the 5-milligram group. And

as a reminder, more than 80 percent of patients in this program were in the 10-milligram treatment group.

Now, to assess dose response, we leveraged our extensive cross-indication knowledge. This table shows the incidence rates for malignancies for 5 milligram and 10 milligram across indications. Again, 5 milligrams blue; 10 milligrams orange. While the rate was numerically higher with 10 milligrams than 5 milligrams, you see these rates do not include the two new cases on 5 milligrams after the data cutoff.

Across indications, we did not observe a dose relationship as shown in the last row of this slide. In RA, the type of malignancy, as was the presentation, was similar to expectations for the population, and when compared to other RA treatments, the rates of a malignancy with either dose fall within the range for biologics in published trials.

Now, to assess risk over time, we again looked to the cross-indication experience with

longer follow-up on 10 milligrams. These are non-cumulative interval rates for malignancy with 10 milligram in RA. The Y-axis is incidence rate, and these rates were calculated at 6-month intervals displayed from left to right. The rate for malignancy remains stable through the observation period of more than 54 months.

If we superimpose psoriasis and UC data on this, when we overlay the rates from psoriasis in yellow and UC in purple across all indications, the rates of a malignancy are stable and similar in magnitude, suggesting no increase in the risk of a malignancy related to tofacitinib over time.

This analysis has excluded non-melanoma skin cancer. As with herpes zoster, NMSC is also a known adverse drug reaction for tofacitinib. In UC, 17 patients had non-melanoma skin cancer. The overall rate of NMSC was 0.84 per 100 patient-years, which is within the range of that reported in Truven. None of these cases were metastatic. Patients had typical risk factors. Most had prior exposure to azathioprine and 6-MP,

and many had a prior history of NMSC.

A similar risk profile for non-melanoma skin cancer was also observed in RA. There was a dose relationship for NMSC. The rates did not increase over time. All but one were non-metastatic, and the rate was within the range of those reported for biologics in published trials.

So far we have talked about infections and malignancies that gastroenterologists are familiar for our RC patients. Next, I will switch to lipid changes.

In the UC program, we saw a dose-dependent increase in several lipid parameters, including total cholesterol, LDL, and HDL, while the ratio of total cholesterol to HDL remained stable. These changes were consistent with the finding in other indications. Changes in lipid parameters stabilized after about 4 to 8 weeks and reversed upon discontinuation. These changes in total cholesterol and LDL respond well to statin therapy. We have also looked into reasons for these lipid level changes, and what we've found is this

increase with tofacitinib is likely due to decreased inflammation and reflects the return pre-inflammatory lipid levels.

Given these laboratory findings, although not expected to increase cardiovascular risks, we assessed for the development of cardiovascular events, and to do that, we looked at major adverse cardiovascular event or MACE, which is a composite endpoint frequently used to assess cardiovascular risk in clinical trials.

In UC, there were 5 MACE events as listed here. Four of the 5 patients reported a medical history of significant cardiovascular risk factors. One patient with aortic dissection reported no serious risk factors in his medical history, and the case resulted in death. The rate of MACE in the overall use experience was 0.25 per 100 patient-years, also within the range of that for TNF blocker in Truven.

In RA, the rate of MACE was about 0.4 per 100 patient-years, and the rates were similar between 5 and 10 milligrams. There was no increase

in incidence rates over time. The rate of MACE with tofacitinib in RA is within the range of those reported for biologics. In addition, when we looked for predictors, we did not find increases in total cholesterol or LDL while on tofacitinib to be associated with occurrence of subsequent MACE.

Lastly, there were 5 deaths in the UC program; 4 were related to malignancies and 1 was related to CV events on 10 milligrams. The mortality rate was 0.24 per 100 patient-years, and this rate is consistent with those in published literature and also consistent with those reported in other tofacitinib indications. While dose response could not be assessed here given a small number of events, we did not observe a dose relationship across the extensive development programs. Events leading to death were consistent with what would be expected in UC based on epidemiological literature.

We also did a comprehensive laboratory assessment and laboratory findings in UC were consistent with RA. First, we did not see a

decrease in hemoglobin. Besides changes in lipid levels as mentioned before, there were dose-dependent changes in several other laboratory parameters. We saw decreases in absolute neutrophil count and absolute lymphocyte count, but only one patient met the discontinuation criteria for ANC, and less than 1 percent of patients met DC criterion for ALC. We also observed increases in CK but without any clinical consequences. These changes were dose dependent and readily reversible after drug discontinuation.

For liver tests, less than 2 percent of patients had single elevations in transaminases at least 3 times the upper limit of normal and less than 1 percent had at least 5 times upper limit of normal. The rates were similar between tofacitinib treatment groups and placebo. There was no Hy's law case and no probable drug-induced liver injury.

Next I will summarize the safety data for each of the three dosing regimens. For the core regimen, the safety profile of 10 milligram was similar to placebo during the 8-week induction

period and the rates of AEs for special interest, for 5-milligram maintenance, were within the range of that for TNF blockers. This data support the 8-week induction with 10 milligram followed by 5-milligram maintenance.

Next, in maintenance treatment in patients who have previously failed TNF blockers, to provide a safety context for benefit-risk discussions, as you will hear in Dr. Corbo's presentation, we first looked at the tofacitinib safety profile in this population alongside TNF naive patients. This slide shows the incidence rates for safety events of interest in the maintenance study. Placebo is in gray; 5 milligrams, blue; and 10 milligrams, orange.

The results shown here include both subgroups of TNF treatment failure and TNF naive patients. The rates were similar between the two patient population, except for herpes zoster and non-melanoma skin cancer where the rates were higher in the TNF failure patients on 10 milligram and the naive patients.

For further contextualization, we asked how does the safety profile of 10 milligram in this TNF failure population stack up against that of comparable patients in the real-world setting? Here are data for only TNF treatment failure patients, orange squares, the 10-milligram group from the overall tofacitinib UC experience, and black triangles are biologics from Truven.

The rates for tofacitinib 10 milligrams were within the range as other UC treatments in Truven with a substantially higher point estimate for herpes zoster. This risk of herpes zoster is a known risk of tofacitinib. It is highlighted in the current package insert, and Dr. Jones will comment on our proposed risk management plan for herpes zoster in his presentation. Together this data support the use of 10-milligram in the TNF treatment failure population.

Finally, the 16-week extended induction regimen. In the UC phase 3 program, patients who did not achieve a clinical response at the end of the 8-week induction could enter the long-term

extension studies who received open-label 10 milligrams. The response was reassessed after another 8 weeks; in other words, after a total of 16 weeks of 10 milligrams.

The question is how does a safety profile with extended 16-week induction compare to that of the 8-week induction? This is the safety data from the 8-week induction cohort with placebo in gray and tofacitinib 10 milligrams in orange. Data shown here are rates for routine safety measures and for AEs of special interest. Displayed alongside in orange striped bars are data from the cumulative 16-week induction with 10 milligrams for the induction nonresponders.

Acknowledging this is not a randomized comparison, the rates for the cumulative 16-week induction are similar to those for the first 8-week placebo-controlled period in gray and orange. This data indicates that the safety profile with extended 16-week induction regimen is similar to that of 8-week induction.

To conclude, the safety profile of

tofacitinib 10-milligram BID for up to 16 weeks in UC patients is similar to placebo. For maintenance treatment with 5 milligrams for all patients and 10 milligrams for TNF treatment failure patients, the safety profile is well characterized and clinically manageable. It is consistent with that observed across indications, including RA, and also similar to that for biologic agents with the exception of a higher rate of herpes zoster.

While we observed a dose dependency for certain safety events, there is no dose relationship for long latency events such as malignancy or MACE. The risk does not increase over time.

We now have an established safety profile of tofacitinib as reflected in the UC program with no new identified risks. At the same time, it is also important for us to expand our existing risk management plan as we bring tofacitinib to a new population. I will now like to turn the presentation over to Dr. Jones, who will describe our risk management plan.

Applicant Presentation - Thomas Jones

DR. JONES: Thank you, Dr. Su.

I'm Thomas Jones, the safety risk management lead for the tofacitinib ulcerative colitis program. I will be providing an overview of the plan for risk management in UC.

Risk management for tofacitinib is ongoing, including more than five years since the first approval for treatment of RA in 2012. The approach we've taken for risk management, with its many facets of pharmacovigilance, has been and continues to be effective in RA and PSA. We've accumulated a wealth of experience. I'll convey how we're relying substantially on this experience in UC. Given the consistency of the safety profile in UC, RA, and PSA, risk mitigation and communication in UC will build on what's already in place for RA and PSA.

All but one of the adverse drug reactions were identified based on data from RA clinical studies. One additional adverse drug reaction, drug hypersensitivity, has recently been identified

from the postmarketing data. No new risks have been identified in the UC program. The risks and safety information for UC on the left side of the slide are already addressed in the product labeling for RA and PSA.

This information is found in several sections, including the box warnings, the warnings and precautions, dosage and administration, and the patient counseling section and the medication guide. In totality, the labeling informs prescribers on considerations before initiating therapy and during therapy, and where appropriate, provides guidance on dose modifications, monitoring, and other topics.

Risk mitigation and communication for UC will build on the approach in RA and PSA. I do want to highlight one difference for UC. Gastroenterologists are a new group of prescribers of tofacitinib, so we plan to reach out to them proactively. We'll do that by providing them with a Dear Healthcare provider letter. The letter will further inform them about the UC indication and the

recommended dosing and the important risks and potential risks, including serious and other important infections such as herpes zoster and also malignancies.

Data collection, assessment, and reporting for tofacitinib in UC will also build on the effective approach in RA and PSA. An important part of that approach is detection of safety signals. Since 2012, several have been open and evaluated and some have led to labeling changes. Ongoing routine monitoring and reporting in RA and PSA will be extended to include UC.

Beyond routine monitoring, the UC safety profile, including long-term use will be further informed by a range of ongoing and planned activities. I'll summarize those activities on the next slide.

First, I'll describe the activities that relate primarily to further assessing safety. Specific to UC, the active surveillance study will prospectively examine safety as observational sources such as claims data potentially

supplemented by electronic health records data. This study will be very well suited for detecting new signals and for monitoring for changes in frequencies of known risks.

The registry will follow patients treated with tofacitinib or with biologics in a natural network of gastroenterology practices using established data collection tools and procedures to validate events. The study will be well suited for evaluating new signals as well as for monitoring changes of known risks. Evidence for any potential dose effects will also be assessed.

A pregnancy registry is planned to assess effects of tofacitinib and pregnancy and associated outcomes. We also are continuing the LTE study to extend our characterization of the safety profile. This is particularly important for assessing longer latency events like malignancies and cardiovascular events.

We are continuing a phase 3B study that just got underway. This study will further inform the safety profile and also assess efficacy of

step-down dosing. An RA activity that will indirectly inform the UC safety profile is an event-driven clinical trial of over 4,000 patients to assess the safety of 2 tofacitinib doses compared with a TNF blocker with primary endpoints of cardiovascular events and malignancies.

Evidence for any potential dose effects will also be assessed. Unlike the UC studies, a substantial proportion of patients are receiving combination therapy with a non-biologic DMARD. I'll also summarize planned studies that relate more to risk mitigation. An observational study will evaluate how both proposed doses are being used. One focus will be to characterize those patients receiving 10 milligrams longer term to assess whether the use aligns with the dosing recommendations in labeling.

Activities will also continue on herpes zoster infection given that it's a well established risk. These activities are relevant. Not only do you see patients, but more broadly to the approved indications and ongoing clinical development

programs. One of the planned herpes zoster activities is a study to assess the safety and efficacy after administration of the newly approved subunit adjuvanted vaccine in patients receiving tofacitinib.

Risk management for tofacitinib in our RA and PSA, with its many facets of pharmacovigilance, has been and continues to be effective. I've summarized these facets as shown on the slide, including risk mitigation and communication, as well as data collection, assessment, and the reporting. The conclusion that risk management has been effective is based on several points.

First, in 2016, FDA agreed the risk evaluation and mitigation strategy communication plan implemented in 2012 had met its goals based on assessment survey findings that showed physicians and patients understood the risk information. Therefore, FDA determined that a REMS was no longer needed. Additionally, we've observed that the frequencies of known risks and potential risks in postmarketing data have generally remained

consistent with the development program studies.

The proposed approach to risk management in UC will build on that effective approach and RA and PSA and on the consistent safety profiles in UC, RA, and PSA. Still there are differences for UC with gastroenterologists being a group new to prescribing tofacitinib and the proposed use of the 10-milligram dose. I've described the specific plan's Pfizer's proposing to help ensure safe and appropriate use of both proposed doses of tofacitinib in UC patients.

We're also committed to a range of robust activities to further inform the safety profile in UC. The safety data that we have been collecting and will continue to collect and assess from those activities enhances our understanding and characterization as a safety profile. We recognize that the ongoing development program studies and post-approval studies that I've described may not detect every conceivable rare event, but we're confident that the risk management activities in place will enable us to respond effectively if a

new rare event is reported in postmarketing surveillance or if the frequency of a known rare event changes.

We use the information and the range activities that I've described to determine the effectiveness of risk mitigation and communication measures, which in turn helps to maximize the favorability of the benefit-risk profile. Noting this critical role of risk management and benefit-risk assessment, I'd like to turn the presentation over now to Dr. Corbo for an overview of the benefit-risk of tofacitinib in ulcerative colitis.

Applicant Presentation - Michael Corbo

DR. CORBO: Our charge in this final discussion will be to place the benefits and risks of tofacitinib in the treatment of UC into context. To accomplish this in part, we will place the data into context using comparisons to existing approved UC therapies at the time of their approval.

As you've seen, the primary posology is for the moderate to severe UC patient who would receive

10 milligrams induction for 8 weeks followed by 5 milligrams of maintenance, and importantly, there are the two options for the extended use of 10 milligrams, which we will discuss further in this. We've utilized a meta-analysis approach to look at the comparative efficacy and safety. The methods we've used are consistent with the most current approaches in the literature, and the FDA supported and encouraged the use of this approach to better inform benefit-risk.

Looking at induction for all patients in the tofacitinib trials relative to the approved therapies, we can see that 8 weeks of induction with tofacitinib provides important clinical benefit. Looking at the TNF treatment failure patients, the differences are more pronounced with tofacitinib being the first investigational therapy to show clear separation from placebo in the induction in this population.

Now to provide context for the risks associated with 10-milligram induction, overall rates of serious infections with tofacitinib were

similar relative to the current UC therapies for induction. While the limited duration treatment with 10 milligrams is on par with other therapies and prior tofacitinib experience, it's important to understand if limited duration of treatment with 10 milligrams has any long-term safety implications. To address this question, we can look into the broader safety database of tofacitinib.

Here, we compared the safety of 482 RA patients initially treated with 10 milligrams of tofacitinib for 3 to 4 months followed by 5 milligrams comparing them to patients receiving 5 milligrams continuously. We've looked at herpes zoster, serious infection, and non-melanoma skin cancer, all three of which we consider to be dose related events and malignancies, which is not dose related.

When we looked through 3 to 4 years of follow-up, the data indicate that limited use of 10 milligram does not appear to have a long-term negative safety consequence relative to 5.

Overall, the safety profile of induction for 8 or 16 weeks for that matter appears consistent with the known profile of Xeljanz, is clinically consistent with the other therapies, and there's no indication of long-term risks associated with limited 10-milligram use. For those events which are unique to tofacitinib, we do have established risk management plans in place and new proposals for UC specifically.

We will now discuss maintenance in the moderate to severe UC patient. Relative to the approved therapies, both the 5- and 10-milligram doses provide clinically meaningful benefit with respect to maintenance of remission. We will now discuss the risks associated with both maintenance doses.

In the case of serious infections, while incident rates are numerically higher for the 10-milligram dose relative to the 5-milligram, both doses are highly consistent with the risk of serious infections relative to approved therapies. When we look at specific infections, we do know

that the rates of herpes zoster are higher than the approved therapies and are dose related.

For malignancies relative to the approved therapies at the time of their approval, the overall risk of malignancies in UC is similar. Now, while this meta-analysis may be deemed reassuring, we need to recognize that rare events carry a degree of uncertainty, which is dependent upon the size and the extent of the database being used. It is important to understand this residual uncertainty relative to benefits that we observe in patients, especially in the context of maintenance therapy.

Uncertainty is not really a tangible metric, however, a way we can try to quantitate uncertainty is to look at a rate event such as malignancies and assess the confidence that we have in a point estimate. Here, we assess malignancies for the 10-milligram dose longitudinally. We can use these data to better understand the residual uncertainty in malignancies, which is represented by the top of the confidence intervals in this data display.

For example, in the RA filing, it was only possible to exclude a relative risk in malignancies of 2.2-fold. However, when we look at the filing for ulcerative colitis today, looking at our cumulative knowledge, given the size and the overall extent of the safety database, we can now exclude a relative risk of approximately 1.15-fold. As such, the remaining residual uncertainty has decreased over time, and we would now consider this to be low.

To summarize the benefit-risk in the core population, given the well established benefit and the characterized and well managed risks, we do consider the benefit-risk for the 10-milligram induction followed by 5-milligram maintenance regimen to be favorable.

Now that we've discussed the core of the dosing regimen, we will look into the options for the extended use of 10 milligrams first in the TNF treatment failure patients. Now, this population is defined by their prior treatment, and as we've already covered induction showing robust efficacy

and acceptable safety, we'll focus on maintenance.

In this population, we can see that the 10-milligram maintenance dosing for tofacitinib does provide meaningful benefit. As shown by Dr. Maller, this dose represents approximately 75 percent relative increase in patients in remission over the 5-milligram, and we see this consistent benefit across multiple measures of efficacy, even all the way through steroid-free remission.

The risks with 10 milligrams have been summarized in the previous figures, and we have identified serious infection: herpes zoster, non-melanoma skin cancer, and certain lab changes to be dose dependent. These are well understood and proactively managed. Also, we have shown that the remaining cumulative uncertainty for malignancies is now low.

While we are committed to inform clinical practice for the most appropriate use of the 10-milligram dose in maintenance, especially in the TNF treatment failure patient population, we need

to make sure that this benefit-risk assessment supports the entire TNF treatment failure patient population to allow physicians and patients to consider dosing with this option through their therapy.

When we've looked at the 10-milligram treatment option in the patient population, we review the overall benefit-risk to be favorable with clear efficacy and well understood risks. We do recognize that some of these risks are dose dependent, and we do think we manage these effectively. But when you consider the high unmet need in this population and the limited options available to them, we do feel that the 10 milligram does provide important benefit.

Now, to discuss the extended induction population, the extended induction population is defined by their clinical response at the end of their initial induction phase of therapy. As noted by Dr. Maller, the extension of some patients to receive an additional 8 weeks of induction can result in a cumulative 75 percent of patients

reaching at least clinical response with tofacitinib, which is clinically important and meaningful when we consider that many of these patients will continue to do well after one year, achieving remission and steroid-free remission.

As noted by Dr. Su and in the meta-analysis, the overall rate and qualitative safety profile of 8 or 16 weeks of inductions were similar, and the short-term use did not appear to negatively impact long-term safety relative to 5 milligrams. As such, we would consider the overall benefit-risk for the extended induction to be favorable.

Now, this is all well and good, but we need to recognize that this will be the first occasion of a 10-milligram approval for tofacitinib, especially when we consider long-term extended use. So the critical question is why now? What's different this time? Well actually, several things are different now.

When we look at this historically, at the time of the RA filing there was a moderate dose response for efficacy in the TNF treatment failure

patients. And while there was and there still is medical need, the residual uncertainty in rare events combined with the moderate dose response and the knowledge that combination use with methotrexate and other disease-modifying immunosuppressant agents would be used, it did not support the approval of 10 milligrams at that time. In psoriasis, while there was a respectable dose response, there was still remaining uncertainty in rare events. And importantly, with the introduction of IL-17 inhibitors and the raising of the bar for efficacy, we did decide to withdraw this filing.

As for PSA, psoriatic arthritis, there was not a clinically meaningful dose response especially in the TNF treatment failure patients, and as such, we did not seek approval for this dose for this disease.

That brings us to today and UC submissions. Here we have a clinically important dose response in the TNF treatment failure patients, primarily dosing without concomitant immune suppressants and

a residual uncertainty in rare events, which is now low. In addition, we have no new safety events, and we have a proven risk management plan in place with enhancements specific to UC proposed.

Also, we proposed additional packaging and labeling options to ensure appropriate use of the 10-milligram dose both within and outside of ulcerative colitis. Importantly, these TNF treatment failure patients have limited options, and an availability of a 10-milligram maintenance dose can be helpful to them and their physicians.

In summary, the qualitative benefit-risks of tofacitinib in the treatment of UC address key needs for UC patients. As Dr. Sandborn discussed, patients need therapies that not only allow for response and remission but also steroid-free remission. Tofacitinib provided substantial benefit in this regard in patients ranging from biologic naive through TNF treatment failure with an onset of efficacy in some patients as early as 2 weeks.

Additionally, tofacitinib offers an

alternative mechanism of action for the treatment of UC, and being a small molecule offers oral administration without the concerns of antidrug antibody development. Also, tofacitinib did demonstrate improvement in quality of life in UC patients, improving not only the manifestations of their disease but their lives as well.

The risks in UC are similar to the other indications and no new events have emerged. The risks are qualitatively consistent between 5 and 10 milligrams, and also these events are well understood and could be effectively managed with the existing and proposed plans.

In conclusion, at Pfizer we are committed to the safe and the appropriate use of our medicines. We have demonstrated this commitment in the clinical development and the postmarketing assessment of tofacitinib in rheumatoid arthritis, psoriatic arthritis, and we will continue this commitment in ulcerative colitis. Most importantly, we are committed to adult and pediatric patients living with UC and hope to bring

a new therapeutic option to them.

On behalf of our team here today, we'd like to thank the committee and the FDA for your attention and thoughtful assessment as we share a common objective in doing the best thing for UC patients. We look forward to answering your questions.

Clarifying Questions

DR. RAUFMAN: We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Chang?

DR. CHANG: It's Lin Chang. Sorry. I'm getting over laryngitis. My questions have to do with trying to figure out when you could potentially -- oh, I guess this would go to Dr. Maller. When can you move a patient from 10 milligrams to 5 milligrams? Because I think, just in general, as a physician, you want to have patients on the lowest most effective dose, not just for this medication but for all medications.

I guess some of the questions that I had was maybe some patients, the 8 weeks induction, if you were on 10 TNF milligrams longer, you could do better on the 5-milligram dose. I guess one thing I was wondering is in the patients who were on the 10-milligram BID maintenance, when they went into the open label and they were randomized to 5 milligrams, how did those patients do? Did they do just as well as the patients on that clinical response at 8 weeks and then went into the maintenance of 5 milligrams?

Maybe some patients need to just be treated longer, and then they could do better on the 5 milligrams to give guidance to physicians that at some point you should try lowering them to the 5 milligram.

Then also, I was wondering if the patients who were in clinical remission -- not just clinical response -- after 8 weeks, and then they went into the maintenance treatment, did those patients do better on the 5 milligram, not just the clinical response? Because you did have some patients,

particularly the TNF naive patients, that did better on the 5 milligram than people who had prior TNF or failures.

So I'm just trying to get a sense of is there a subgroup of patients that if you treat them longer on 10 milligrams, they could be moved to the 5 milligrams, or patients who had a clinical remission or were not on TNF before, they were not TNF failures, that those patients could go on a 5 milligram for the maintenance.

DR. SU: Let me address your second and third question, and we'll circle back to the first question. Our program was designed looking at the maintenance study for 52 weeks. At the end of 52 weeks, the only patients that received 5 milligram in the long-term extension were those patients who were in remission at the end of the 52-week maintenance study.

So those patients who were receiving 10 milligrams in maintenance, who subsequently went into the maintenance study in the long-term extension on 5, they were in remission at the end

of the 52-week maintenance, and approximately 70 percent of those patients were still in remission at the end of one year in long-term extension. But this was a particular subpopulation of those who were already in remission at the end of one year.

Our induction study, the pivotal study, was designed to limit exposure of a placebo to 8 weeks for those patients who had moderate to severely active UC program. We did not want to expose those patients for more than 8 weeks as we thought that may be too long for those patients.

Now, I want to circle back to your very first question in terms of when to transition from 10 milligrams to 5 milligrams. For the trial, what I can tell you is how we designed the trial. In the trial, in the programs, the criteria, the threshold for moving from induction to maintenance, was a clinical response, not remission. We recognize both the response and remission were important efficacy measures, but for induction, a clinical response was what we focused on.

We know that you heard from Dr. Sandborn that induction was about clinical response so that patients can continue on treatment where they could potentially gain further improvement and possibly remission during the maintenance. I will ask Dr. Sandborn to give his perspective on how to set the patient goal.

DR. CHANG: You're not answering my question, though. My question was, in the patients on 10 milligrams of maintenance who were in clinical remission, who went to the open label 5 milligrams, how many of those patients were maintained in remission? That's my first question, which I didn't get the answer to.

My second question is, there are patients who reached clinical remission at 8 weeks. They were randomized. They must have been in the group that got the 5 milligrams in maintenance. I want to know how well they did versus the patients in clinical response.

DR. SU: So to the first part, patients from induction, only the nonresponders would go directly

into the open label, so they could only get 10 milligrams. The only patients that received 5 milligrams in the long-term extension were those patients who completed the 52-week maintenance study and were in remission at the end of 52 weeks. Those were the only patients who were able to receive 5 milligrams.

DR. CHANG: Could someone else answer that question? I know you guys have that data or maybe you could search for the data. Does anyone else understand my question?

DR. CHANG: Yes. I will also ask Dr. Maller to address the question in terms of our data from the maintenance study, which is the second part of your question in terms of patients who were in remission at the end of induction, who went into the maintenance study.

DR. MALLER: Eric Maller, Pfizer clinical. If I understand, we would look at patients who went into induction for the first part of your question, got 10 milligrams, randomized to 5 milligrams in maintenance, and then how did they do subsequently

once they went down to 5 milligrams. Correct?

DR. CHANG: No. I'm asking the patients on 10 milligrams during maintenance, how did they do in the open label on 5 milligrams?

DR. MALLER: Sorry. Could I have slide EF-9 up? Patients received 10 milligrams or placebo in induction. The responders went in and those randomized to 10. Again, if you are randomized to 10 and you were in remission, you had to be in remission at the end of maintenance, then you got 5. So if you were only in response, you still got 10.

As you can see on the left for remission, month 2, 81 percent still had remission; 73 percent by a year. When you look at response, you get about 93 percent maintenance of response and 85 percent at month 12.

DR. CHANG: Thank you. To me, this looks like potentially there are patients, that if you treat them longer on 10 milligrams, you could move them to 5 milligrams. You really only tested initially on 8 weeks of induction on clinical

response, right?

Do you have data on the patients, the subset in 8 weeks, who were in clinical remission. You do have patients because you showed data on that. If they were randomized to the 5 milligram, if they did better than if you had a clinical response at 8 weeks.

DR. SU: What I would like to do is actually ask Dr. Maller to come to the lectern and maybe go through the design of the program and respond to in terms of what we see in the maintenance study in terms of the results for those patients who are in remission versus not in remission at baseline of maintenance. And I would still like to ask Dr. Sandborn to give his perspective in terms of your questions maybe longer and then go down to 5.

DR. MALLER: Eric Maller, Pfizer clinical. Qualitatively, as you might guess, those who enter maintenance and remission overall do better than those who enter in response regardless of dose.

Let's show slide EF-144. This is a subgroup analysis across the primary and key secondary

endpoints as well as clinical response based on baseline remission yes versus baseline remission no. Of course, baseline remission no are the patients I think you might be interested in also, the ones who just achieve response. All remitters are of course responders.

You see that 10 performs better than 5 no matter which subgroup you're in, but in terms of the absolute rates, you can see that if you're in remission, for instance remission at week 52, 56.6 versus 34.2 for the remission no; 5 milligrams, also a decrement, 46.7 versus 25. So qualitatively it's the same, but quantitatively of course the responders don't do as well as those who are in remission.

DR. SANDBORN: Dr. Chang, I think it's a very good question. The way that I would think about this is, first of all, for patients that are not failures, nobody's talking about chronic 10, so just only the failure patients. And among those, if we could bring up slide MA-46 to begin with, here's the naive patients, and you can see the

difference between 5 and 10 is low and the difference between both doses and placebo is big. So why would you continue 10 in this patient population when it looks like 5 will do the job? That's off the table. No one's proposing that.

Then if we could go to slide MA-47, this is the heart of the matter. If you look at the failure patients, the difference between drug and placebo for remission at the end of the year is 10 percent, and that's actually with nominal p-values not statistically significant. Then the difference between 5 and 10 with nominal p-values actually is statistically significant, and the difference between placebo and the 10-milligram dose is big.

So if you turn this into number needed to treat, it's about 10 for the 5-milligram dose and it's about 3 for the 10-milligram dose over the course of the next year. So it seems to me not right to push patients down to 5 milligrams in the short term, which I would call a year -- that's what this trial was -- because they do so much

better in this failure patient population on 10 milligrams.

Now, the question you're asking, we can't quite answer, is that at some point in time are these patients who got 10 milligrams for a year going to take 10 milligrams for 5 years? And the truth of the matter is probably not. Actually, in the long-term extension, patients are now being randomized to chronic dosing with 10 to drop down to 5 versus continuous. So we'll get some data about that eventually. We just don't have it yet.

You're very active in medical education. If you think about the IBD lectures everywhere, everyone always talks about deescalation, but it's not deescalation in the first 6 months or so; it's the idea that as you get into a full remission, then you're looking at deescalation 6 months to a year into treatment. And for all the other drugs we have, that ends up being a clinical judgment scenario.

If you think about TNF blockers, the trial designs are exactly like this. You induce

response, you randomize the responders to the drug or placebo for a year, and then clinicians will figure out when they want to deescalate therapy, whether it's dropping the concomitant immunosuppressant or sometimes stopping the biologic after a year, but it doesn't get legislated.

To me that's the clinical question, and I think practitioners are going to be very sensitive about this. And since we have some evidence of 5 milligrams, I'll bet -- and what I'm going to do is look at patients over time, and as they get into a deep remission, then you would probably look at backing off. I just don't want to be pushed into that early on because the difference is so much better for efficacy over the course of a year in the failure patients, and only the failure patients. I don't think we'll be using 10 milligrams in naive patients.

DR. RAUFMAN: Thank you. Dr. Grayson?

DR. GRAYSON: Mitch Grayson. I have a question actually for Dr. Su about the zoster. And

I don't know if you have these data or not, but in terms of the 5 milligram and the 10 milligram, is there any difference or how long does it take to clear the zoster? We have the incidence of zoster occurring, but how quickly are they able to clear the zoster? I assume they stop the drug when they have zoster in the trials. If you could explain that.

DR. SU: To clarify, in the program, those patients who had serious infections would be required to be discontinued, but then other patients would continue on the treatment. And in fact, in the UC program, more than 90 percent were able to continue the treatment.

As far as how long it takes to resolve, I will ask Dr. Valdez, who leads the overall development program, to talk about our experience from not just UC but also RA and other indications.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. We have analyzed and time to resolution of the herpes zoster event among patients who participated in the tofacitinib development program, and the

best data we have is the data from the rheumatoid arthritis development program as it has the largest number of patients who experienced that herpes zoster event.

Slide SA-122 up, please. In the rheumatoid arthritis development program, the mean time to resolution of an event of herpes zoster was 35 days. As it has been described in the literature, patients who had a more limited disease at 1 dermatome involvement tended to have faster resolution than patients who actually had multidermatomal involvement. Slide down, please.

During the tofacitinib development program overall, we suggested but did not mandate treatment with antiviral therapy, and 20 percent of the patients in the psoriasis development program actually did not receive antiviral therapy. We also analyzed those patients, and we saw that those patients using the immune system on its own resolved the herpes zoster events, but there was an advantage to using antivirals with about 5 days to the resolution.

DR. RAUFMAN: Thanks. You I assume don't have a comparison between it? Those studies were the 5 milligram in RA, so you don't know if 10 milligrams made a difference in terms of time to clearance, do you?

DR. SU: The RA program also had both 10 and 5, and the information, the data results were consistent with similar.

DR. RAUFMAN: Okay. Thanks. Dr. Fuss?

DR. FUSS: Actually a follow-up question to Dr. Grayson's question concerning herpes zoster. In the patients who did develop herpes zoster, did you measure total immunoglobulin levels? And the reason I ask that is in patients with IBD, we could have a loss of proteins specifically through the gut and specifically at immunoglobulin levels.

As tofacitinib can decrease generation of various T and B cells as noted in your handout, did we have a decrease in immunoglobulins? If they were measured, were they due to a loss or were they do also to a decreased generation of the ability to make plasma type cells that could generate

immunoglobulins?

I don't know if you have that data. The reason I asked that, the last part, the most significant, if you're looking to use a herpes zoster vaccination in these patients, if the drug is knocking out their cells and ability to make immunoglobulin, the vaccination may not prove fruitful.

DR. SU: To address whether we did it in the UC program, the answer is no. But we understand herpes zoster is an important outcome, and we have done extensive analysis looking at the patients and also the potential impact of herpes zoster. I will bring, again, Dr. Valdez to describe what has been done mainly in other indications.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. We had a phase 2 study in patients with rheumatoid arthritis in whom we wanted to test actually the safety and immunogenecity of the older herpes zoster vaccine, Zostavax, the live vaccine. So we looked at patients who had rheumatoid arthritis and were receiving corticosteroids and methotrexate and

were about to start on tofacitinib, as they were failing methotrexate.

The study, the sign is as shown, SA-61, please. SA-61 up. So these patients who were failing methotrexate, receiving methotrexate and corticosteroids, were immunized with a zoster vaccine approximately 14 days before starting tofacitinib or placebo. Then we analyzed immunologic responses, both antibody responses, and also cell-mediated immune responses, which are thought to be the effector protecting against herpes zoster, both at week 4, that is 4 weeks after vaccination and 2 weeks after initiation of tofacitinib, and at week 12, so 3 months after immunization with Zostavax.

What we found is actually the antibody responses that we observed among patients who received tofacitinib were similar to the antibody responses, BCV, specific igG responses, among patients who will receive placebo. And actually when we compare those humoral responses to patients who have participated in the licensing studies of

Zostavax, they were similar.

Also, when we analyzed the cell-mediated immune responses using the whole virus as a stimulus, we found that the cell-mediated immune responses in both the tofacitinib and placebo arm were similar, and there were somewhat lower than what's observed in the licensing studies of Zostavax. Given the advantages of the new subunit adjuvanted vaccine, we are proposing to studies this purportedly more effective vaccination to see if it's safe and effective in people with autoimmune diseases.

DR. RAUFMAN: Thank you. Dr. Proschan?

DR. PROSCHAN: I had a couple of questions. One was concerning TNF failure patients versus non-failure. I'm assuming that someone has done an interaction test of dose versus whether you failed TNF, and I'm assuming that that test did not come out statistically significant or I think we would have heard about it. So that's my first question.

The second question was about failing at 8 weeks and then going on for 8 more weeks on

10 milligrams. You're attributing this change in improvement from 39 percent to 75 percent as being because of the tofacitinib, but in fact we don't know what would have happened if you had taken patients who failed 8 weeks and randomly assigned them to 5 or 10. My understanding is that's not what happened.

So we don't know if you had switched them to 5, you would have seen a similar change, or for that matter, we don't even know if you'd switched them to placebo, which I wouldn't -- I understand why you didn't do that, but whether we would have also seen a change because part of it is just a regression to the mean effect. If you're requiring patients to have failure at 8 weeks, then part of the reason for failure is measurement error whenever you're measuring something.

So why did you not randomly assign people who failed 8 weeks to go down to 5 versus continued on 10?

DR. SU: I'll address your second question followed by the first question. To address your

second question, why did we not randomize patients who failed 8-week induction to continue on 10 milligrams versus 5 milligrams, or even placebo, we designed our induction study to limit exposure to placebo to these patients for 8 weeks. We knew from our data that 5 milligrams we expected to be less efficacious than 10 milligrams, and for that reason we did not either study placebo control for 16 weeks nor randomized to those patients who already failed 8-week induction to a lower dose. We recognized that was a non-randomized comparison.

In terms of the relevance of those data, I will ask Dr. Sandborn to come and answer from his clinical perspective the relevance of those data. But to answer your first question and take that first, I will first ask our clinical pharmacologist, Dr. Arnab, to the lectern to provide those results because we did look at the other interactions.

So Dr. Arnab first to address the first part of the question in terms of the interactions of the TNF treatment failure, and Dr. Sandborn next to

give his perspective in terms of the clinical relevance of our induction nonresponder extended 16-week data.

DR. MUKHERJEE: We looked at it from an exposure-response perspective where we did not find an interaction. I'll ask Dr. Wenjin Wang, who's our statistician, to address your question around the interaction.

DR. WANG: I'm Wenjin Wang, biostatistics, from Pfizer. We did look at the interaction, but you need to realize this study is not powered to detect interaction, [indiscernible] is small. The p-value is not significant but it's small. I would like to emphasize again, when we look at this group, the upper row, you see that 10 milligram is better than 5. When we first examined the TNF failure subgroup, you can see the majority of the difference between 5 and 10 came from TNF bronchial failure subgroup.

DR. SANDBORN: Your question about trial design is exactly on the mark. In a perfect world, if we could turn back the clock, that's probably

what we should have done or could have done. The question is what to do with the data that we have and what are the ways of interpreting it.

So there are a couple of ways of interpreting it. One is to say it's observational data and do the best that we can with it. One would be to say, okay, remember these patients have centrally read endoscopy, and the failure patients in particular have a pretty poor prognosis. So we would imagine that the natural history of those patients would be to significantly improve during the next 16 weeks or the next 8 weeks, and in general that is not the case.

So one way of looking at this would be to just think about what the rates of response were during the second 8 weeks relative to the placebo rates during the first 8 weeks. It's not an ideal comparison for sure, but that would be one way of doing it. I think we might have a slide like that if we could bring it up.

The other way of doing it would be to say, okay, so what's the historical placebo rates in

clinical trials? That I think is problematic because the placebo rates in this trial will be in the context. Many of the previous studies would have not had TNF blocker failures in them, and those placebo rates are a lot lower. And there wasn't centrally read endoscopy for qualification of patients, and that tends to inflate the placebo rates over time.

So I would feel not very comfortable about doing a meta-analysis of other moderate-severe trials, placebo rates, and trying to compare against this. I think from a clinical perspective, I feel most comfortable just acknowledging the limitations of the lack of a control observationally.

If we could bring up slide MA-55. Out of the gate you have 57 percent of patients responding to 8 weeks of induction therapy with 10 milligrams, and then of the patients who didn't respond, if you treat them for another 8 weeks, with all the limitations, that it's open-label data, but remembering the endoscopy piece of this is actually

centrally read, so you could think of that as perspective observer-blinded endpoint data. It's not subject to bias and 50 percent of the nonresponders responded. That's a really big number, and my belief is that it's bigger than what you would see if you had a control arm. Then that adds an absolute 16.5 percent to the total responding numbers, which in this patient population is a really large number.

So the challenge for the committee will be to think through these are limited data, but if it's real, the effect size looks clinically meaningful. So what's the safety cost to going an extra 8 weeks? And you heard from Dr. Su a few minutes ago that the safety over an additional 8 weeks looked very much like the first 8 weeks, and whatever the safety signals are come late in the course, they're not really coming during the first 16 weeks.

So as you trade off how to turn clinical trials into clinical practice in the context of what will get approved, these data, which are

encouraging but have some statistical limitations, vis a vis what the safety trade-offs would be, that's why you guys are here.

DR. RAUFMAN: We're going to need to move ahead, and we'll get to other questions later on. We'll now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at about 10:30 a.m.

(Whereupon, at 10:27 a.m., a recess was taken.)

DR. RAUFMAN: We will resume. Before we move to the FDA's presentation, we'll take just a couple of more questions. I encourage both the questioners and the responders to please stay focused and keep the questions and answers as focused and brief as possible. Dr. Assis on the phone has a question.

DR. ASSIS: Hi. This is Dr. Assis. I have a question for Dr. Jones who earlier presented a risk mitigation strategy talking about the need to

educate GI providers, that this is a new medication for them. I was struck by one of the cancers that was found with this drug having been a cholangiocarcinoma. That highly suggests to me that there was a patient or more who had primary sclerosing cholangitis, which is associated with ulcerative colitis, and it's a very high risk condition for cancer.

The question is, has the applicant considered education and instructions for potential GI prescribers to screen for PSC because that would certainly not be an unheard of complication, and lack of recognition of a subpopulation with UC that could develop malignancies would be unfortunate to miss.

DR. SU: Before I bring Dr. Jones up, just one clarification. In the UC program, we excluded patients who had evidence of PSC from the program

DR. ASSIS: Sure. What I would just say to that is that I think that in the community particularly, there probably are patients who have PSC, and in addition there's a recent trial which

suggest that even the rates of PSC are higher than the standard diagnosis based on symptoms. So that could be an increasing problem once it's prescribed out in the community.

DR. JONES: Thomas Jones, safety risk lead, Pfizer. I appreciate the point that there are a number of background factors that could influence the manifestation of risks or potential risks. I spoke specifically to providing a gastroenterologist with a Dear Healthcare provider letter that would focus on the identified risk and potential risk but would not get specifically into further background risk information. However, those are plans.

We're very open to working with FDA and reviewing those plans and refining any further educational efforts such as the Dear Healthcare provider letter. So again, those are not intended to be necessarily final form, and the point is taken that there could be additional information.

DR. RAUFMAN: Thank you. Dr. Strate, you had a question.

DR. STRATE: This is for Dr. Su and has to do with herpes zoster. I know there have been a lot of questions, but one thing that Dr. Sandborn brought up is that in GI, we're used to managing patients with multiple medications that increase the risk of infection, including dual therapy and immunomodulators alone. And I'm wondering if in the Truven data where you compare data to people who've received TNF, if there's any data on dual therapy or any data on azathioprine alone that might put this into context for clinicians.

DR. SU: We had limited data, but I will ask our epidemiologist, Dr. Geier, to provide further details of our Truven data.

DR. GEIER: Jamie Geier, Pfizer epidemiology. So of course we used the Truven database, a claim database, to help contextualize what we are seeing within the clinical program. And while we use different techniques, including stratifying the patient population by our inclusion/exclusion criteria and working with endpoints with predefined and validated algorithms,

we did not dig into past therapies specifically. So I don't have that information for you for herpes zoster, but that's certainly something that can be queried at a later date and provided.

DR. RAUFMAN: Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. Regarding the indication for treating for 16 weeks of 10 milligrams BID among initial nonresponders, could the applicant comment on the precedence of relying on open-label extension data for efficacy in that group? I know that this has been touched upon, without a placebo group it is hard to extrapolate, but it is worth pointing out that the placebo response for the phase 2 study was more than 40 percent.

DR. SU: We recognize the data, there was no control group for our open-label data. What we did see, as you heard from Dr. Maller's presentation, when we look at those patients, more than half of them achieved the clinical response and that efficacy was sustained over time. I think in terms of what that means from the clinical perspective, I

will ask Dr. Sandborn to give his comments, especially in terms of how that is viewed from a clinical perspective and the historical data.

DR. SANDBORN: We've talked about this already, but let's bring up slide EF-187. This looks at the change in partial Mayo score over time, so you're seeing it at 4 weeks and 8 weeks according to what happened. You can see in the orange that patients who are getting 10 milligrams BID, they're nonresponders and then go into open-label extension; that they have this drop in the partial Mayo score. And remember, the partial Mayo score, unlike the full Mayo score, has a range of 0 to 9, so this is on average a 2-point drop.

Then the patients who went on to placebo, you can see a rise in the patients who were on 10 milligrams and went into the placebo-controlled trial. So they withdrew, and you're following them for another 8 weeks. They're sort of worsening. And then you have the placebo responders who went on to placebo maintenance, and those are a special group of patients anyway because they responded to

placebo.

So you can see that in patients who've responded to drug and withdrew it, that they actually worsened by almost 2 points, and the patients who responded to placebo, and of course the patients you're talking about were the nonresponders, that even the patients who responded to placebo, a special group of patients, their disease activity was rising, whereas the patients who went on to get drug, their disease activity dropped.

If you look at the difference between patients who got the second 8 weeks of drug and their numbers dropped versus the patients who went on to placebo having responded, the difference between them is 4 out of a scale of 9. So we're not going to get a perfect answer on this, but this gives you a little bit of a sense that maybe the placebo rate wouldn't have been so high in those patients, and therefore the 50 percent response rates that we saw, at least part of that is real.

The other thing is to think about what

happens -- and could we bring up the slide that shows -- Dr. Maller showed it earlier. It shows the long-term outcomes of the patients that had gotten the extra 8 weeks of induction. Remember on the left, of the nonresponders -- bring up MA-52. Of the nonresponders, 51 percent of them responded with an extra 8 weeks, again, with minimal implications for safety. And then if you look out over a year, 73 percent of them maintained clinical response and 45 percent of them were in remission and steroid-free remission.

We usually don't think of -- you could argue they could bounce around a little bit in the short term, although I'm not so sure. But to see this durability in those patients, this feels like something different than just placebo natural history to me.

DR. RAUFMAN: Thank you. Dr. Khurana?

DR. KHURANA: Sandeep Khurana. I just need, quick, two clarifications. One is, was there seen a difference of response based on gender and ethnicity? And number 2, did the dose response

correlate with extent of disease?

DR. SU: The short answer to both questions is no. We have examined the various factors, including those that you mentioned, and we did not see a difference.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: Jenifer Lightdale. Dr. Su, if you can answer two questions that I hope are brief. One is, did you measure fecal levels of the molecule? Building on other biologics, we know in more severe disease you can find higher levels of the biologics in the poop. That's question one. Question 2 is did you look at immune status of the patients going in, in terms of I'm sure TB, but also CMV, BCV, EBV, et cetera?

DR. SU: To your first question, fecal calprotectin, we did not collect that in --

DR. LIGHTDALE: No, not fecal --

DR. SU: Oh, fecal drug.

DR. LIGHTDALE: Yes.

DR. SU: Okay. No, we did not. We did not, the stool level, the drug level. The second

question is in terms of checking for -- and I want to clarify in terms of whether we measured levels such as CMV levels and EBV viral load levels. We did not do that for UC. We have done that in the phase 2 RA in the psoriasis program; clinically no change with CMV viral load. With EBV viral load, we had 3 patients that had levels above 500 without any symptoms.

DR. RAUFMAN: Dr. Fuss?

DR. FUSS: A quick question to Dr. Su actually, and a follow-up question to Dr. Assis. Were exon sequencing or genetic analysis done on any patients, especially those who had developed carcinomas? And a follow-up to that is patients who have JAK3 mutations or IL-7 receptor mutations could have some of the types of abnormalities, specifically the malignancies, that you saw and may explain possibly the decreased efficacy versus malignancy rate.

So were any exon sequencing performed on those patients or the general population and is anything planned specifically for the pediatric

population to use as an exclusion of monogenic type disease in that type of population?

DR. SU: We did not do genetic testing of sequencing in the UC program, either prospectively or any particular patients based on their outcomes. We do have samples, and we are looking into exploring further analysis on that.

As far as the pediatric program, you will hear that we are working with FDA currently to develop our study, so that in terms of what we will be doing and proposing in terms of excluding perhaps some and showing that patients had genetic testing for the very early onset of disease, that is still being developed.

DR. RAUFMAN: The last question before the FDA presentation, Dr. Lane?

DR. LANE: Are there any biomarker data that might be helpful in looking at this difference between 5 and 10 milligrams?

DR. SU: The only biomarkers we looked at in phase 3 was CRP, and we saw a decrease in CRP with treatment as expected. We did look at, quite

extensively -- in terms of trying to refine patients, we did in TNF treatment failure patients to see if we can identify perhaps if there are additional subpopulations who would do better with 10 than 5. We looked at over 1300 different combinations of baseline characteristics and demographics, and we were not able to find anything clinically meaningful.

But at the same time, and to get to your question, we did try to look for are there patients who may do poorly. And what we did find was that there are certain patients -- a trend where some patients who seemed to be doing poorly on 5 milligrams, TNF treatment failure patients doing poorly, and that includes patients who had residual elevated CRP at the end of induction.

DR. RAUFMAN: We will now proceed with the presentations from the FDA.

FDA Presentation - Lesley Hanes

DR. HANES: Good morning. My name is Lesley Hanes, and I'm a medical officer from the Division of Gastroenterology and Inborn Error Products

within the FDA Center for Drug Evaluation and Research. This morning we have heard and appreciated the introductory remarks from FDA clinical team leader Dr. Tara Altepeter and the applicant's presentations regarding their tofacitinib ulcerative colitis program. At this time, the following presenters will provide FDA considerations.

Clinical pharmacology reviewer Dr. Dilara Jappar will present our perspective on the program's dose evaluation and selection. Mathematical statistician Dr. Sara Jimenez will provide a statistical evaluation of the efficacy data and results for the applicant's proposed dosing regimens.

Following, I will present a focused review of potential dose-dependent safety signals observed in the UC program; then epidemiology medical officer Dr. Joel Weissfeld will provide remarks about the use of Truven MarketScan database results for comparison to the tofacitinib related safety risks. Finally, medical officer Dr. Melanie

Bhatnagar will present considerations for the planned tofacitinib UC program for pediatrics.

As previously expressed, we are grateful for the committee's insights, questions, and guidance today.

Dr. Jappar?

FDA Presentation - Dilara Jappar

DR. JAPPAR: Good morning, everyone. My name is Dilara Jappar. I'm a clinical pharmacology reviewer in the Office of Clinical Pharmacology in CDER. Today I will discuss the major clinical pharmacology findings of tofacitinib in the UC development program, which were reviewed by myself and Dr. Fang Li, who is a pharmacometric reviewer in the Office of Clinical Pharmacology.

Today my discussion will focus on the exposure comparison of tofacitinib in the UC population with other disease populations that were previously evaluated followed by the dose selection rationale for phase 3 induction studies. Lastly, we will discuss the exposure response analysis for efficacy in the maintenance trials.

Pharmacokinetics of tofacitinib in patients with moderately to severely active ulcerative colitis were characterized by population PK approach based on sparse PK samples that were collected from one phase 2 dose-ranging study and three phase 3 trials in UC patients. As shown in this table, following 5-milligram BID dosing, the systemic exposure at the steady state in UC populations were comparable to that of patients with plaque psoriasis and psoriatic arthritis and about 20 percent lower than that of patients with rheumatoid arthritis. Following the 10-milligram BID dosing, the systemic exposure of tofacitinib in UC patients were again similar to that of patients with plaque psoriasis and psoriatic arthritis.

Next we will talk about the dose selection rationale for the phase 3 induction trials. In order to find the optimal dose for induction of remission for UC, the applicant had conducted a randomized, double-blinded, placebo-controlled, parallel group, phase 2 dose-ranging study in patients with UC with 8 weeks of treatment

evaluating 0.5-milligram dose, 3-milligram, 10-milligram, and 15-milligram dose levels. Please note that 5-milligram dose was not included in this phase 2 dose-ranging induction study.

The results of the dose-ranging phase 2 study had shown that there's a dose-dependent increase in clinical response, the primary endpoint, and the clinical remission, the secondary endpoint. The clinical remission reaches plateau at 10-milligram dose where the dose response for 10 milligram and 15 milligram was similar.

Based on the result of the phase 2 study results, the applicant had chosen 10-milligram and 15-milligram doses to be further evaluated in the phase 3 induction trials. However, shortly after the initiation of phase 3 trials, the applicant had discontinued the 10-milligram [sic – 15-milligram] dose and focused on evaluating 10-milligram BID dose for induction of remission in phase 3 trials.

Furthermore, when the relationship between induction of clinical remission at week 8 and the exposure were explored, where the X-axis represents

the average plasma concentration of tofacitinib at various dose levels and the Y-axis represents the probability of achieving clinical remission, the model predicted probability of achieving clinical remission increased with increase in plasma concentration and reached a plateau at a concentration that reflects about 10-milligram BID dosing, supporting the selection of 10-milligram BID dose as the induction dose for phase 3 induction studies.

In conclusion, the observed dose response and exposure response relationship in phase 2 dose-ranging trials supported the selection of 10-milligram BID dose for induction of remission in phase 3 trials.

As noted previously, the 5-milligram dose was not included in the phase 2 dose-ranging induction study. Given the prior safety concern with 10-milligram BID dosing, it raises the question whether 5-milligram dosing would have been as efficacious as 10-milligram BID dose.

To address this question, the agency and

applicant tried to predict the efficacy at the 5-milligram BID dosing by developing an exposure-response model for efficacy using pooled data from the phase 3 induction studies. The model-predicted remission rate for placebo and 10-milligram BID dose was consistent with observed remission rate confirming the validity of this model.

With this model, the predicted remission rate at 5-milligram BID dose was 12.8 percent while the remission rate at 10-milligram BID dose was 19.1 percent. As the difference between the predicted remission rate at the 5-milligram dose and 10-milligram dose was considered to be clinically relevant, it was concluded that the 10-milligram dose was likely to result in better clinical efficacy compared to 5-milligram dose in terms of induction. Therefore, the applicant's selection of 10-milligram BID dose for phase 3 induction trials were further supported by modeling and simulation of the remission rate at 5-milligram BID dose.

Thus far, we had discussed dose selection rationale for induction phase. For maintenance of UC remission, the applicant did not conduct a separate phase 2 dose-ranging study. Rather, in their phase 3 maintenance trial, the applicant had evaluated two dose levels of the 5-milligram dose and 10-milligram dose to find the optimal dose. Now we will switch gears and discuss exposure-response analysis for efficacy in the maintenance trial.

Following 8 weeks of treatment from two phase 3 induction trials, all clinical responders, which included patients who reached remission and also patients who did not reach remission at the end of 8 weeks treatment, were all enrolled into 52-weeks long maintenance trial. The probability of achieving remission at the end of this 52-week treatment was model predicted based on the remission status at baseline as an exploratory analysis.

The graph on the left represents the patients who are remitted at baseline, whereas the

graph on the right represents the patients who were not remitted at baseline. As you can see from both graphs, regardless of remitter status at baseline, the 10-milligram dose appeared to give numerically higher probability achieving remission at week 52 compared to 5-milligram dose. However, the clinical relevance of this numerical difference is unclear and will further be discussed by our colleagues in the context of risk-benefit ratio given that the 10-milligram dose appears to be associated with higher risk for certain adverse events of special interest compared to the 5-milligram dose.

As the applicant is proposing 10-milligram BID dose as the maintenance dose in UC patients who are prior TNF blocker nonresponders, the probability of achieving remission at week 24 and week 52 were model predicted based on the TNF blocker response status as an exploratory analysis.

For TNF naive responders, at week 24 and week 52, the relationship between probability of achieving remission and systemic exposure was

almost flat between 5-milligram dose and 10-milligram dose although 10-milligram dose did give numerically higher probability of achieving remission compared to the 5-milligram dose.

For TNF blocker nonresponders, at week 24, the 10-milligram dose did not give any higher probability of achieving remission compared to 5-milligram dose. Nevertheless, at week 52, 10-milligram dose did give numerically higher probability of achieving remission compared to 5-milligram dose. However, the slightly higher probability of achieving remission in TNF blocker nonresponders was only achieved after long-term use for 52 weeks, not at 24 weeks. Nevertheless, clinical relevance of this small numerical difference is unclear and will further be discussed by our colleagues in the context of risk-benefit ratio.

In summary, the systemic exposure of tofacitinib in patients with UC was comparable to that of patients with plaque psoriasis and psoriatic arthritis and about 20 percent lower than

that of patients with rheumatoid arthritis at both dose levels, the 5-milligram dose and 10-milligram BID dose. The observed dose-response dependent increase in the clinical remission rates supported the selection of 10-milligram BID dose for induction treatment in the phase 3 trials.

In the maintenance treatment, 10-milligram dose showed a numerically higher remission rate at 52 weeks compared to the 5-milligram dose regardless of baseline remitter status or prior TNF blocker responder status. The clinical relevance of this small numerical difference will be further discussed by our colleagues in the context of risk-benefit ratio.

With that, I'd like to conclude my talk and welcome the next speaker, Dr. Jimenez, to discuss the efficacy data for the proposed dosing regimen.

FDA Presentation - Sara Jimenez

DR. JIMENEZ: Hello. I'm Sara Jimenez from the Office of Biostatistics at CDER. Today I'll discuss an overview of studies in the new drug application, dosing regimens for ulcerative colitis

and evidence regarding the applicant's additional dosing regimens for two subgroups. This includes induction nonresponders and TNF blocker failures.

First, and overview of the NDA. The applicant submitted data from a single phase 2 dose-ranging trial, study 1063; two phase 3 induction trials, studies 1094 and 1095; a single phase 3 maintenance trial, study 1096; and long-term safety data from an open-label extension study, study 1139. Studies 1094 and 1095 were identical 9-week studies and study 1096 was a 52-week study for subjects who had completed study 1094 or 1095 and had achieved at least a clinical response in those trials.

Results for studies 1094 and 1095 primary and key secondary endpoints at week 8 are shown here. The differences in responder proportions compared to placebo ranged from 10.3 to 16.8 percent. P-values for all the endpoints were highly significant.

Results for study 1096 primary and key secondary efficacy endpoints at week 52 are shown

here for the prespecified analysis population, the full analysis set. P-values for all the endpoints were highly significant for both study drug dosages. For the primary endpoint, the differences from placebo seen in both study drug groups were close in value, 23.2 and 29.5 percent, however, the effects of the tofacitinib 5-milligram BID and 10-milligram BID doses were not statistically different for primary and key secondary endpoints at a nominal alpha level of 0.05.

Next, I'll discuss dosing regimens. The applicant's prespecified tofacitinib dosing regimen for adult patients with moderate to severely active UC is 10 milligrams BID for induction for 8 weeks and 5 milligrams BID for maintenance. The applicant's results for the prespecified endpoints in this dosing regimen were statistically significant.

The applicant included additional dosing regimens for two subgroups. First, for patients who do not achieve adequate therapeutic benefit by week 8 or the induction nonresponders subgroup, the

induction dose of 10 milligrams BID can be extended for an additional 8 weeks, or 16 weeks total, followed by 5 milligrams BID for maintenance; discontinue therapy in patients who do not achieve adequate therapeutic benefit by week 16.

Second, for patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to TNF blocker therapy, 10 milligrams BID for maintenance may be considered in order to maintain therapeutic benefit. Refractory patients are defined as those with a history of prior TNF blocker failure.

Next, I'll discuss induction nonresponders with a focus on patients in that subgroup who received 16 weeks of tofacitinib 10 milligrams BID. The applicant conducted an exploratory efficacy analysis that included patients in studies 1094 and 1095 who did not achieve clinical response by week 8 and who were then treated with an additional 8 weeks of tofacitinib 10 milligrams BID in the open-label extension study 1139.

Patients in this group may have received

either 8 weeks of tofacitinib 10 milligrams BID for those initially randomized to placebo during induction or 16 weeks of tofacitinib 10 milligrams BID for those who initially received blinded active treatment during induction.

Because in clinical practice no one will receive placebo for 8 weeks, the following discussion focuses only on the population in the second bullet, those patients who received active treatment in study 1094 or 1095 but failed to have a clinical response and then continued with active treatment for the additional 8 weeks, resulting in a total of 16 weeks exposure to 10 milligrams BID for induction of remission.

The following applicant-generated table summarizes efficacy results for patients in this induction nonresponder subgroup who initially received active treatment in study 1094 or 1095; that is only the patients who received 16 weeks of active tofacitinib therapy.

These results are shown since patients with initial nonresponse to placebo may not be

comparable to those who had nonresponse to active treatment. Also, the goal of analysis was to explore whether the applicant's proposal to continue induction dosing to 16 weeks for those who failed to initially respond is adequately supported.

Study 1139, overall remission rates based on locally and centrally read endoscopies, were similar to placebo remission rates in comparable UC clinical trials. The analysis on locally read endoscopies, which had no comparator group, suggests that for patients failing to respond after 8 weeks induction therapy, continuing therapy for 8 additional weeks resulted in rates of remission at month 2 of approximately 14 percent. When this population was followed longer term, results suggest low proportions of patients in remission by 12 and 24 months. Remission rates at 12 and 24 months were approximately 25 percent.

Of note is that within the tofacitinib UC program, overall response rates were noted to be slightly higher based on local reads when compared

to central reads for the time points for both evaluations were available. Also, although comparisons to placebo response rates in UC at one year in other development programs are somewhat limited by differences in study populations' design and conduct, available data suggests that placebo remission rates at 52 weeks are still substantial, ranging from 8.5 to 17 percent in various estimates.

The analysis on centrally read endoscopies, which also had no comparator group, suggests that for patients failing to respond after 8 weeks induction therapy, continuing therapy for 8 additional weeks resulted in rates of remission at month 2 of approximately 9 percent. For those with prior TNF blocker failure, the remission rate was lower at 6.2 percent. For those without prior TNF blocker failure, the remission rate was 12.4 percent.

To provide context, estimates of placebo remission rates in controlled clinical trials for UC vary but are in the range of 5 to 12 percent for

induction. Also, remission rates for induction for the prespecified primary endpoint were between 16 and 19 percent.

In summary, these exploratory results on data with no comparator group indicate that remission response rates in the induction nonresponder group, after 16 weeks of tofacitinib therapy and longer term, were similar to placebo response rates in other controlled clinical trials for UC. These results are consistent with what we would expect from placebo treatment.

We note the limitations in comparisons to other UC clinical trials but also note that these subgroup analyses had no concurrent comparator group. Thus, these results do not provide adequate support for the applicant's assertion that extended induction therapy for induction on responders provides meaningful benefit.

Next, I'll discuss patients with prior TNF blocker failure. The applicant conducted exploratory efficacy analyses by prior TNF blocker failure. Patients in the prior TNF blocker failure

subgroup in studies 1094 and 1094 had smaller remission rates at week 8 compared to the subgroup without prior TNF blocker failure as shown here.

Note that remission rates for induction for the prespecified primary endpoint were between 16 and 19 percent. In the subgroup with prior TNF blocker failure, remission rates were about 11 percent. Also, the induction studies only had tofacitinib 10 milligrams BID and placebo groups, so the effect of tofacitinib 5 milligrams BID is not known.

Additionally, the 5-milligram BID and 10-milligram BID doses in study 1096 did not differ statistically at week 52 regardless of prior TNF failure as shown here for the full analysis set, the prespecified analysis population; that is, for both tofacitinib dose levels, the differences in proportions of subjects who were in remission at week 52 compared to placebo were smaller in the subgroup with prior TNF blocker failure compared to the subgroup with prior TNF blocker failure.

Note that remission rates for the

prespecified primary endpoint were between 34 and 41 percent. In the subgroup with prior TNF blocker failure, remission rates ranged between 24 and 37 percent.

In the subgroup of patients who did not have prior TNF blocker failure, the differences in remission rates compared to placebo were numerically very similar between tofacitinib dose levels, 30.7 and 33.2 percent in the 5- and 10-milligram groups, respectively. However, in the subgroup with prior TNF blocker failure, the difference in proportion of subjects in remission at week 52 compared to placebo in the tofacitinib 10-milligram BID arm was about twice that of the 5-milligram BID arm, but this apparent difference between dose levels observed in this analysis was not nominally statistically significant. The nominal p-value was 0.07.

It should be noted that in these subgroup results, a small sample size and wide confidence intervals emphasize the fact that the treatment effect estimates are not precise and not reliable.

Also, exploratory results cannot be relied upon for dosing recommendations.

My colleagues will describe further concerns associated with the tofacitinib 10-milligram BID treatment. Thus, in the three phase 3 studies, smaller proportions of subjects in remission were seen in the subgroup with prior TNF blocker failure. The applicant is proposing a tofacitinib dosing regimen for subjects with prior TNF blocker failure.

These exploratory results do not provide evidence for a difference of treatment effect between the tofacitinib dose levels in the subgroup with prior TNF blocker failure. Also, in study 1096, there is uncertainty regarding comparison of the 10-milligram dose to the 5-milligram dose. Results suggest that the treatment effects for both doses do not differ.

In summary, the maintenance efficacy of tofacitinib 5 milligrams BID, in treating adults patients with moderate to severely active UC after 8 weeks induction of tofacitinib 10 milligrams BID,

has been demonstrated. The benefit of the long-term use of tofacitinib 10 milligrams BID compared to tofacitinib 5 milligrams BID has not been demonstrated. And finally, given the safety issues that my colleagues will discuss, we have concerns that the applicant's exploratory analyses were not adequate to support the two additional dosing regimens. Thank you.

FDA Presentation - Lesley Hanes

DR. HANES: Hello. I will be presenting the FDA perspective on safety concerns observed in the tofacitinib program for the treatment of patients with moderate to severe ulcerative colitis. Today, for the committee's considerations, focus will be given to potential dose-dependent risks with the use of the higher 10-milligram dose of tofacitinib in comparison to the lower 5-milligram dose. For simplification, these twice-a-day dosages will be referred to as 10-milligram or 5-milligram dose.

In general, in the interest of protecting patients from possible and avoidable harm with the use of medications, both the efficacy benefits and

safety risks of proposed drugs, their doses, and regimens are considered in the process of drug approval. Therefore, our aim is to select the lowest effective drug dose and corresponding regimen for patient treatment.

In the tofacitinib program, we recognize that both the 5-milligram and 10-milligram doses were found to be efficacious for long-term UC treatment. However, as you will hear, we have identified possible dose-dependent safety risks with the use of the higher 10-milligram dose in comparison to the lower 5-milligram dose.

To frame this discussion, the box warning for tofacitinib, also known as Xeljanz, lists significant safety risks for patients that should be noted. Risks such as serious infections, tuberculosis, and opportunistic infections, as well as malignancies, including lymphomas have led to patient hospitalizations or even death.

The Xeljanz label also includes multiple warnings of precautions regarding its use in the setting of active serious infections. The warning

and precautions section also details the potential for GI perforations and the need for laboratory monitoring for potential hematologic, liver enzyme, and lipid level changes. Also included is a recommendation to avoid immunizations with live vaccines.

Given the severity of these known safety risks, we will discuss the following this morning: a brief safety related history of tofacitinib dosage; the safety results of the phase 3 randomized 8-week induction trials; and the evaluation of the proposed 16-week extended induction treatment regimen; limitations to the safety analyses based on the overall UC program design; adverse events of special interest and higher risks that were observed with the 10-milligram dose treatment after induction; and finally our summary and benefit-risk considerations will be provided.

The tofacitinib 10-milligram twice a day dose has not been FDA approved for any inflammatory disease indication, however, as you are aware, the

lower 5-milligram dose is approved for the treatment of patients with rheumatoid arthritis and psoriatic arthritis.

As you've heard, tofacitinib has been studied in greater than 7,000 patients with RA with an exposure of approximately 22,000 patient-years as of March 2017. At the time of tofacitinib approval for RA in 2012, dose-dependent safety risks included tuberculosis, malignancies excluding non-melanoma skin cancers, and laboratory abnormalities within hematologic liver enzyme, creatinine and liver, and lipid parameters.

These risks created a concern for possible over-immunosuppression with the use of the 10-milligram dose for long-term treatment. In addition, the Xeljanz label includes information regarding a patient who met Hy's law criteria for drug-induced liver injury while receiving treatment with the 10-milligram dose.

A long-term post-approval safety outcome trial in RA patients is ongoing for particular adverse events of special interest as required at

the time of original approval of tofacitinib. In this randomized controlled trial, the safety risks of the 5-milligram and 10-milligram doses are being evaluated regarding uncommon and possibly latent events such as malignancy and major adverse cardiovascular events.

I will now direct your attention to the patient experiences observed in the UC program and the safety of the applicant's proposed 8-week and 16-week induction treatment regimens. We concur that the phase 3 randomized induction trials demonstrated that the safety of the 10-milligram dose for short-term, 8-week treatment appears to be acceptable and comparable to the placebo group's safety profile.

The percentage of patients who experienced a serious adverse event, or SAE, was 4 percent in the tofacitinib treatment group in comparison to 6 percent in the placebo group, and most of these adverse events were gastrointestinal or infection in nature.

For those who did not respond to the initial

8 weeks of induction, an additional 8 weeks of 10-milligram treatment was given in the open-label study as extended induction treatment for a total of 16 weeks. SAEs occurred in 5 percent of this cohort, and their safety profile also appeared to be comparable to those treated with the initial 8 weeks of tofacitinib. However, we note that a randomized concurrent controlled group did not exist for the comparison of safety with a select subgroup of patients.

Prior to discussing potential dose related safety risks, I direct your attention to the safety analysis limitations that are secondary to the program's design. As seen in this graph, the UC program's design led to an imbalance of dosage exposure and the number of patients categorized in each dose group for analysis.

The predominant dose analysis cohort is depicted by the green bars and includes all the patients who received tofacitinib 5-milligram or 10-milligram dose in the UC program. As of September 2017, 83 percent of patients were

categorized to the predominant dose 10-milligram group with an exposure of approximately 1500 patient-years. In stark contrast, only 17 percent of patients were categorized to the predominant dose 5-milligram group with an exposure of approximately 500 patient-years.

Patients were categorized based on their average daily tofacitinib dose received during their entire treatment course, which may not correlate with the actual dose that was given before or around the time of experienced adverse events. Furthermore, the post-induction dose analysis cohorts are presented in the lower bars. Categorization was more restrictive and was based on the patient's dose received for a period of time after the induction trials. Not all the patients who received tofacitinib were included in this analysis set, therefore the predominant dose analysis groups were used primarily for our risk evaluation.

In addition to these limitations, the agency acknowledges a shortcoming observed in a

demographic group of patients. Patients whose race was identified as black comprised only 0.8 percent of the entire UC safety population, which is much smaller than the proportion with the disease in the U.S. population. In the maintenance trial, only 2 patients of this demographic group were treated with tofacitinib.

As you can see here, a similar imbalance between dosage analysis groups was noted for patients who had prior TNF failure. In general, the differences in the sizes and dose exposure of the 5-milligram relative to the 10-milligram group raises concerns that the ability to detect uncommon adverse events may not be comparable.

The randomized controlled maintenance trial, which allowed for direct comparison of the safety profiles of both doses over 52 weeks, had analogous limitations. Only patients who achieved clinical response in the phase 3 induction trials were randomized to one of the three arms. Therefore, patient exposure to each dose was possibly too small to capture uncommon adverse events of special

interest.

The open-label extension study had safety analysis issues as well. There were a limited number of patients allocated to the 5-milligram group since only those who achieved remission at the end of the maintenance trial were treated with a 5-milligram dose in the open-label study. This allocation affected the severity of UC disease in both dosage groups.

The median Mayo scores at the study's baseline were 9 for the 10-milligram group versus 1 for the 5-milligram group, therefore, disease severity was inherently greater in those treated with the higher dose in comparison to the lower dose in the extension study. We also note that a large number of patients in the UC program discontinued treatment in both groups.

I will now discuss possible dose-dependent imbalances observed within the UC program for select adverse events of interest. However, as we have acknowledged, most of the patients in the UC program were treated with the higher tofacitinib

dose and that these patients had greater disease severity in the long-term extension trial, which could confound the interpretation of dose-risk comparisons.

The applicant has concluded that there are higher dose-dependent risks for the following adverse events: herpes zoster infection, serious infections, and non-melanoma skin cancers. Based on safety data from this and other tofacitinib programs, we agree with this assessment, and we believe that there may be additional dose-dependent risks observed within this UC program.

These include patient deaths and malignancies, excluding non-melanoma skin cancers; herpes zoster related opportunistic infection; possible drug induced liver injury; and adverse cardiovascular and thromboembolic events; as well, changes in particular liver laboratory values also including lipid levels, creatinine, CPK, and decreases in absolute lymphocyte and neutrophilic counts.

In the UC program, 5 deaths occurred in

treated patients. The causes of death are shown in this table along with the cumulative days of drug exposure. Four of the 5 deaths were related to malignancies or related complications. Note that all deaths occurred in patients treated predominantly with the 10-milligram dose. As previously described, we recognize that most of the patients in the UC program were treated with the high dose long term.

At the time of the September 2017 data cutoff, malignancies were diagnosed and adjudicated in a total of 28 patients. We acknowledge that these numbers differs slightly from those presented by the applicant, as the results of additional malignancy cases have been recently reported to the agency. Patients with these cancers were classified and evaluated in two separate groups. The first group looked at malignancies that excluded non-melanoma skin cancers, and the second group included these types of cancers.

Within the UC program, 13 patients had a total of 15 adjudicated malignancies that excluded

non-melanoma skin cancers. We note that all these patients were treated predominantly with the 10-milligram dose and were diagnosed in the long-term extension study.

In the predominant dose 10-milligram group, there was an instant rate of .084 per 100 patient-years. Additionally, of these patients, 92 percent had prior azathioprine or 6-MP exposure, and 77 percent had a history of prior TNF failure. We acknowledge that those exposed to TNF blockers or immunomodulators may have increased risk for the development of cancer, which further complicates our ability to understand the association between tofacitinib treatment and malignancy.

The tables on this and the next slide summarize the malignancies diagnosed in patients and the tofacitinib doses received in the UC program. We know that 2 patients developed adenocarcinoma of the colon and that cancers associated with infections such as EBV and HPV were also observed.

Here are details regarding additional

patients with malignancies. As you can see, patients primarily received the 10-milligram dose as shown in red. This graph shows the time course of the diagnosis of adjudicated malignancies. Only the 10-milligram group is shown since there are no events that were adjudicated in the 5-milligram group at the time of the September 2017 cutoff date.

For the second group of malignancies, 15 patients had adjudicated non-melanoma skin cancers. Similar to the RA program, non-melanoma skin cancer is recognized as a dose-dependent risk in the UC program. For this and first event, the incidence rate ratio was 1.3 for the 10-milligram versus 5-milligram group, therefore there is an estimated increased risk of 30 percent roughly for the diagnosis of these cancers in those treated predominantly with the higher versus lower dose. For the characteristics of these patients, 14 out of 15 had prior exposure to azathioprine or 6-MP; 13 out of 15 had prior TNF failure, and 7 out of 15 had a prior history of non-melanoma skin cancer.

As presented in this table, there are a total of 5 cases of adjudicated cardiovascular events in the UC program. The patients' treatment courses are presented here and 4 of the 5 patients had received the 10-milligram dose at or before the time of their events. Given the known dose-dependent increases in lipid levels with tofacitinib, including LDL, observations of major adverse cardiovascular events are of special interest. However, the FDA's assessment of whether drug-induced increases in LDL levels affect cardiovascular risk is outstanding and we await results from the ongoing long-term safety trial in RA patients.

We note that thromboembolic events had been recognized in patients treated with JAK inhibitors. In the UC program, 4 patients treated with tofacitinib had pulmonary embolism events in the open-label extension study. All these patients were predominantly treated with a 10-milligram dose, and one of these patients died from the embolism in the setting of malignancy. In the UC

program, there were no occurrences of observed deep-vein thrombosis in patients treated with tofacitinib.

I will now briefly discuss select laboratory abnormalities observed within the UC program. For both doses, laboratory abnormalities were similar to those noted in the Xeljanz label. These include potential dose-dependent decreases in absolute lymphocyte count and absolute neutrophil count and increases in lipids, creatinine, CPK, and liver enzyme levels.

As mentioned earlier, a Hy's law case of drug-induced liver injury involving the 10-milligram dose is included in the Xeljanz labeling. Accordingly, based on prespecified elevated liver enzyme signals, 5 patients in the UC program were identified with liver injury that did not meet Hy's law criteria and were mild to moderate in severity. These cases were adjudicated by the program's hepatic enzyme review committee as having a possible likelihood of drug-induced liver injury.

The designation of possible likelihood means that the committee was confident to a certain degree that tofacitinib treatment was the cause of the concerning liver enzyme elevations versus other risk factors. While each of these patients were analyzed as part of the predominant dose 10-milligram group, again, we recognize that most patients were allocated to this analysis group.

In the UC program, a modest dose-dependent decrease in absolute lymphocyte count was observed in patients. At the baseline of the program, no patients had a confirmed ALC of less than 1,000, however, there are patients who had confirmed post-baseline decreases. ALC less than 1,000 were seen in approximately 20 percent of patients in the 10-milligram group versus 17 percent in the 5-milligram group. Also, a small number of patients in both treatment groups met the criteria for discontinuation, the confirmed ALC less than 500 based on the Xeljanz label recommendations.

Although the pattern of recovery from low lymphocyte count was established in patients within

the RA program, this has not been well described in the UC patient population. We are also concerned that low absolute lymphocyte count as caused by tofacitinib may be associated with increased risks of serious infections.

Finally, I will present infection risks in the UC program as it relates to tofacitinib dosage. The risk of infection occurrence is a major concern with tofacitinib use as noted in the Xeljanz label. Here's a figure of the cumulative percentage of patients experiencing infections over time in the UC program. The upper line represents the 10-milligram and the lower line represents the 5-milligram analysis group.

A dose-dependent risk of serious infections was identified in the overall UC program. Three percent of patients had infections that met criteria for serious adverse events. The comparison of the incident rates per 100 patient-years for serious infection for the 10-milligram versus the 5-milligram group creates an incident rate ratio of 1.4, therefore, there is an estimated

increase in risk of 40 percent roughly for serious infection in patients predominantly treated with the high versus low dose.

Regarding opportunistic infection risk, these adverse events occurred infrequently and were adjudicated in approximately 2 percent of the patient population. Of these infections, 18 cases were herpes zoster related opportunistic infections such as disseminated herpes zoster, which occurred in 6 patients, including one person who developed herpes zoster meningoencephalitis, 2 patients who developed ophthalmologic infections, and 3 patients who had multidermatomal infections. And as described by the applicant, non-herpes zoster opportunistic infections occurred in 4 patients.

Here's a figure of the cumulative percentage of patients experiencing herpes zoster infection over time in the UC program, which is recognized as a dose-dependent risk. The upper line represents the 10-milligram and the lower line represents the 5-milligram analysis group.

Finally, this table shows the number of

patients with prior TNF failure who experienced herpes zoster and opportunistic zoster infections in the maintenance trial. Although the occurrences of these adverse events were few in the maintenance trial, probable dose-dependent relationships exist in this patient subgroup.

In conclusion, I will now provide our summary and benefit-risk considerations. There were multiple limitations and challenges in the safety analysis for the overall comparison of dosage risk in the UC program. The majority of patients were evaluated in the predominant dose 10-milligram group as compared to the 5-milligram group. Overall, the severity of disease was greater in those treated with the higher versus lower dose, and high rates of discontinuation in both dose groups further limited the ability to detect uncommon and potentially latent safety events.

This slide summarizes benefit-risk considerations. We acknowledge that both the 5-milligram and 10-milligram doses of tofacitinib

demonstrated efficacy for long-term ulcerative colitis treatment. As previously discussed by our statistical reviewer, Dr. Jimenez, the UC program was not designed to establish whether treatment with the higher dose was more efficacious than the lower dose. We agree with the applicant's assessment that there are dose-dependent risks for herpes zoster infection, serious infections, and non-melanoma skin cancers. Moreover, we have identified potential dose-dependent risks such as malignancy and death.

In general, this presentation discusses our interpretation of the safety results by dose based on the UC program's data. Whether safety risks that may be dose dependent outweigh the potential benefit of the long-term use of the 10-milligram instead of the 5-milligram dose remains uncertain.

I thank you again for your considerations and attention this morning. At this time, my colleague, Dr. Joel Weissfeld, will address concerns regarding the use of the Truven MarketScan claims database for the comparison of

population-based risks to those observed within the tofacitinib UC program. Thank you.

FDA Presentation - Joel Weissfeld

DR. WEISSFELD: My name is Joel Weissfeld. I'm a medical officer in the CDER Office of Surveillance and Epidemiology or OSE. OSE prepared the following remarks about the applicant's use of the Truven MarketScan claims database for external comparison.

Truven captures data submitted to U.S. health insurance companies or Medicaid by healthcare providers or patients requesting payment for medical care delivered or received. In addition to the identity and quantity of drugs dispensed by pharmacies, Truven captures diagnosis and medical procedure codes associated with inpatient and outpatient healthcare encounters.

The applicant used diagnosis, procedure, and drug codes in Truven to identify adult UC patients currently or previously treated with a drug generally regarded as medically appropriate for moderate or severe UC. The applicant defined a

5-year study period ending in September 2015. The Truven UC population analyzed by the applicant contained 6,366 patients, mean age 43 years, 52 percent male.

To focus discussion, OSE restricts all subsequent commentary to the safety outcome of malignancy other than non-melanoma skin cancer. In 4,420 patients with a drug or procedure code for a TNF alpha blocker, infliximab, adalimumab, or golimumab, the applicant used an undisclosed code set to observe 31 malignancy events over 4,895 patient-years of follow-up. Using these results, the applicant estimated risk for malignancy in the moderate to severe UC population at 0.6 per hundred patient-years.

OSE lacks complete understanding of the methods used by the applicant to estimate risks in Truven. Nevertheless, OSE regards the 0.6 per hundred patient-year malignancy risk estimate as reasonably credible and consistent with results derived from medical literature and other sources, including SEER, the Surveillance Epidemiology and

Results program managed by the National Cancer Institute. Therefore, OSE can accept the estimate from Truven if used for the appropriate purpose.

OSE regards the results from Truven as estimates of the background risks for malignancy and possible other outcomes in the clinical population of interest, adults with moderate to severe UC. These estimates of background risks might contribute to an understanding of results observed in the tofacitinib UC safety population. From Truven, for example, we understand that malignancy occurs in patients with moderate to severe UC, and background risks in moderate to severe UC might explain the number of patients observed with malignancy in the tofacitinib UC safety population.

In the appropriate setting, OSE might accept Truven as a data source for an internally controlled study of drug safety. However, to study the comparative safety of tofacitinib relative to a treatment alternative such as TNF alpha blockers, OSE would require more stringent methods than those

used by the applicant.

The applicant also advises consideration of the differences between the two distinct data sources when comparing trial data against Truven. Truven describes outcomes observable in a real-world setting, whereas the tofacitinib UC safety population describes outcomes observed in a clinical research setting.

Other challenges to interpretation include inadequate control for confounding; that is important baseline differences between the tofacitinib UC safety population and the study population defined in Truven; markedly different methods for defining, ascertaining, and validating malignancy outcomes and other outcomes; and statistical uncertainty presented by the few malignancy events observed in both the tofacitinib UC safety population and the study population defined in Truven.

Therefore, OSE recommends that the advisory committee avoid using Truven to conclude that tofacitinib at any dose is less safe, as safe as,

or safer than TNF alpha blockers. Thank you for your attention.

FDA Presentation - Melanie Bhatnagar

DR. BHATNAGAR: Good morning. My name is Melanie Bhatnagar. I'm a medical officer in the Division of Pediatric and Maternal Health at FDA, and I'm going to spend the next 15 minutes or so talking to you about the pediatric ulcerative colitis program for tofacitinib. Really, the purpose of this presentation is to provide some relevant background information related to pediatrics and to describe the applicant's proposed pediatric study plan.

FDA is seeking comments from the advisory committee regarding this proposed plan in the context of the safety concerns that have been identified in the adult UC program, particularly those related to serious infections and malignancies that were described at the morning presentations.

I will start by providing a brief overview of the relevant pediatric drug legislation and some

general information about JAK inhibitors in pediatrics to put the applicant's proposed plan into context. Next, I'll describe the applicant's proposed plan, as well as FDA's current thinking about how to evaluate products for treatment of pediatric ulcerative colitis.

We'll start with the pediatric legislation that's relevant to this pediatric development program. The 2003 Pediatric Research Equity Act, or PREA, gave FDA the authority to require pediatric data to assess the dosing, safety, and effectiveness of a drug or a biologic product for the same indication that's being sought in adults, unless that requirement is waived or deferred.

Pediatric study requirements under PREA apply whenever the product contains any of the features that you see underlined on this slide, so a new active ingredient indication, dosage form, dosing regimen, or route of administration. PREA requires sponsors to submit an initial pediatric study plan, or IPSP, typically following the end of phase 2 meeting for the adult program.

So really, the overall concept here is that sponsors are required to provide information about the use of their product in the pediatric population, and we want to start the conversation about the best way to obtain that information very early in the drug development process so that children are not an afterthought.

This slide will show how FDA has applied PREA to JAK inhibitors. There are currently two JAK inhibitors approved by FDA for use in adults, and that's ruxolitinib and tofacitinib. For ruxolitinib, FDA granted orphan designation for the two approved adult indications you see listed here, and under our statute, PREA requirements do not apply to product indications which have been granted orphan designation.

Tofacitinib is the only JAK inhibitor that has been subject to pediatric study requirements under PREA. Tofacitinib as you know is approved in adults for psoriatic arthritis and rheumatoid arthritis, and of course the applicant is currently seeking adult approval for this third indication of

ulcerative colitis.

For the psoriatic arthritis indication, the applicant received a waiver of PREA requirements because the condition is extremely rare in the pediatric population. However, PREA did apply for the rheumatoid arthritis indication, and at the time of approval in 2012, FDA issued pediatric study requirements to assess the safety and effectiveness of tofacitinib in pediatric patients 2 years of age and older with juvenile idiopathic arthritis or JIA, and those studies are currently ongoing.

PREA also applies to the current application to expand tofacitinib use to adults with UC, and as such, the applicant was required to submit an initial pediatric study plan, the IPSP, detailing their proposal for assessing the safety and effectiveness of tofacitinib for treatment of pediatric UC. So here I want you to see the opportunities to obtain information about the use of JAK inhibitors in the pediatric population have been limited, so there's minimal experience using

these drugs in children. That leads me to a brief discussion about the mechanism of action of JAK inhibitors and how that may be important for their use in children.

Here you can see a representation of the very complex JAK signal transduction pathway, and this representation shows 7 receptors in the cell membrane. This includes receptors for interlukins, interferon, erythropoietin, and each of these is associated with a Janus kinase. Once these receptors are activated, the signal transducers cross the nucleus and effect changes in gene transcription.

This JAK signal transduction pathway is an essential cascade for mediating normal functions of various cytokines in the development and the function of the hematopoietic and immune systems. Inhibition of this pathway may lead to decreased immune functioning and may limit the body's ability to protect from infectious and malignant entities. The precise effect the inhibition of this pathway may have on the normal development and function,

particularly in younger pediatric patients with developing immune systems, is not known.

Here you can see a very simplistic timeline of immune system development. Although substantial changes to the immune system take place very early in life, from birth to 2 years of age, the immune system continues to evolve into school age and does not approach adult capacity with that more robust adaptive immune memory until the teenage years.

The ability of the immune cells to produce and respond to cytokines varies throughout the early stages of development. For example, monocytes reach the adult capacity to produce TNF and IL-6 near 3 years of age, and dendritic cells, which produce interferon and interlukin-12, reach adult numbers near 5 years of age.

Non-clinical toxicity studies of tofacitinib in juvenile animals at the human equivalent age of 2 years have demonstrated a decrease in red blood cells, granulocytes, and lymphocytes, as well as lowering of thymus and spleen organ weights with treatment. As Dr. Hanes noted, approved

tofacitinib labeling does caution prescribers that tofacitinib use has been associated with laboratory abnormalities in adults, including neutropenia, lymphopenia, and anemia.

We'd like you to consider how inhibition of cytokine signaling with the use of tofacitinib may further limit the ability of a younger pediatric UC patient to respond to infectious entities given their immature innate immunity as well as their inexperienced adaptive immune memory.

We've discussed the pediatric legislation, which prompted the requirement to establish a pediatric UC program for tofacitinib, and we've briefly looked at the mechanism of action of JAK inhibitors and highlighted our limited experience with these drugs in the pediatric population. So with this background information in mind, I'll next describe the applicant's proposed pediatric UC plan for tofacitinib.

The applicant submitted their initial pediatric study plan in March of 2014, and this plan describes a single study of the safety and

effectiveness of tofacitinib in pediatric patients 4 years to less than 18 years of age with moderate to severe ulcerative colitis who have had an inadequate response to prior therapies.

The applicant subsequently submitted a pediatric study protocol in January of this year. Although FDA has not yet fully reviewed the study protocol, I will highlight two changes the applicant has proposed related to the maintenance pediatric dosing regimen and the lower age limit for study enrollment.

The proposed study consists of an 8-week, open-label induction phase followed by a randomized, placebo-controlled, double-blind, 44-week maintenance phase in those who achieve clinical response or remission during induction. An open-label, 52-week extension study will also be conducted to assess long-term safety.

Patients will be enrolled stepwise with adolescents 12 years to less than 18 years of age enrolling first to obtain PK dosing information followed by patients less than 12 years of age.

Tofacitinib will be provided as an oral tablet or as an oral solution, and dosing for pediatric patients will be weight based and will target the exposures equivalent to those achieved in adults.

The planned pediatric induction dosage will be targeted to match exposures achieved in adults who received 10 milligrams twice daily. For pediatric patients entering the maintenance phase, it will be randomized 1 to 1 to 1 to placebo or to one of two active treatment groups to match adult exposures of either 5 milligrams or 10 milligrams twice daily.

In the applicant's proposed protocol, the plan for dosing in the induction phase remains the same, however, the randomization and dosing strategy for the maintenance phase will remain the same only for pediatric patient weighing 30 kilograms or more. Based on PK information obtained in that pediatric JIA study, the applicant predicts that the maximum steady state drug concentration, or Cmax, achieved in pediatric patients will increase with decreasing body weight

when targeting the average drug concentration achieved in adults.

The applicant notes that pediatric patients weighing less than 30 kilograms are predicted to have up to a 2-fold higher Cmax relative to adult patients at an equivalent dose. Therefore, the applicant proposes that patients weighing less than 30 kilograms be randomized 2 to 1 to 5 milligrams twice daily or placebo to avoid that substantially higher Cmax in these patients during maintenance treatment.

The applicant does acknowledge that these lower weight pediatric patients will be subject to a higher Cmax during the 10-milligram induction phase but justifies the exposure based on the shorter induction duration of 8 weeks and the presumption that exposures less than that may be inadequate to achieve a response.

In the study protocol, the applicant is proposing to study pediatric patients down to 2 years of age based on FDA's current requirements for studying pediatric UC, but the applicant had

originally planned to request that FDA waive their PREA requirement to study patients less than 4 years of age on the basis of safety. Although these safety concerns are theoretical and are not substantiated with evidence, I'll mention them for the purposes of the discussion today.

The applicant had suggested that the more extensive and severe disease seen in younger pediatric patients with UC may increase their susceptibility to bacterial translocation across damaged intestinal mucosa and that these patients may develop more severe sequelae of bacteremia if they're receiving an immunomodulator such as tofacitinib given their potentially immature immune systems and additional immune suppression related to their disease.

Now that we have an understanding of the applicant's proposed pediatric plan, I'll briefly describe FDA's current thinking about studying products intended to treat pediatric UC. FDA considers the pathogenesis of UC to be similar between adults and pediatric patients. The

pediatric patients tend to have greater disease severity with more extensive colonic involvement and higher rates of colectomy when compared to adults.

FDA currently requires an assessment of the safety and effectiveness of products intended to treat UC in pediatric patients down to 2 years of age unless a specific safety reason exists that would preclude studying these patients. Generally, one adequate and well controlled pediatric UC study is acceptable if the response to the drug is similar between adults and pediatric patients such that FDA may partially rely on the efficacy findings in the adult program.

An important need for therapies for pediatric UC exists. For pediatric patients with UC that's refractory to corticosteroids 5-ASA and thiopurines, infliximab, a TNF blocker, is the only approved next line of therapy. Here you can see a table showing these three TNF blockers and the single integrin receptor antagonists that have been approved for a UC indication alongside the proposed

UC indication for tofacitinib. Infliximab is indicated for induction and maintenance treatment in pediatric UC patients 6 years of age and older, and the remaining products are approved only for use in adult UC.

All of these products require either an IV infusion every 8 weeks or a subcutaneous injection every 2 to 4 weeks for maintenance therapy. If approved, tofacitinib would provide the only option for an orally administered late-line therapy in these pediatric UC patients and of course would target a separate signaling pathway than the other products.

In summary, information on the use of JAK inhibitors in the pediatric population is limited. The ongoing study of tofacitinib in the pediatric JIA study is the only study that has been initiated under PREA for a JAK inhibitor. Pediatric UC tends to be more severe compared to adults, with higher rates of extensive colonic involvement and an increased likelihood for needing a colectomy.

The applicant proposes studying pediatric

patients 2 years of age and older with moderate to severe UC at dosages targeting adult exposures of up to 10 milligrams twice daily for induction and maintenance. The apparent dose-dependent safety findings in adults, including malignancies and serious infections, raise concerns regarding the appropriate population and dosage to target in the pediatric UC study. Thank you for your time.

Clarifying Questions

DR. RAUFMAN: Thank you. We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Jonas?

DR. JONAS: Thank you. This is Beth Jonas from UNC. My question is regarding some of the safety data that we talked about in terms of infection. On slide 77, we see that 20 percent of patients in the 10-milligram group demonstrated decrease in absolute lymphocyte count, and there is a concern that this may somehow predict the development of an infection, specifically a viral

infection.

My question is, are there data that support that? In other words, was the low lymphocyte count associated with a higher risk of infection?

DR. HANES: That's a great question. The applicant did provide some modeling data, and I'm going to refer that question to the applicant to give some information about their modeling.

DR. SU: We do have data from rheumatoid arthritis that showed low ALC less than 500 is associated with increased risk of serious infection but not associated with herpes zoster or malignancies. I can ask Dr. Valdez to provide further details of those data.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. Can I have SA-64, please? Because of the size of the rheumatoid arthritis development program, we were able to conduct multivariate analysis to ascertain what were the risk factors for developing a serious infection in these patients. And what you see in this slide are the results of a Cox regression model.

The most important risk factor for development of a serious infection was in fact actually a confirmed lymphocyte of less than 500. That is why in that current label, we suggest discontinuation of tofacitinib in patients in the monitoring lymphocytes and discontinuation of tofacitinib in patients who actually developed a lymphocyte count of less than 500.

We also see that there are other risk factors that modulate the risk of developing serious infections such as the use of corticosteroids being a diabetic and the tofacitinib dose. And we see, very consistent with FDA analysis of ulcerative colitis that, increasing risk of infection by increasing tofacitinib dose by 5 milligrams is about 39 percent.

Slide down, please. We have performed the same analyses for the development of herpes zoster, and we do not find a cut-point for a heightened risk of herpes zoster by lymphocyte count, although there is a relatively -- a slight linear relationship and an increase of risk of herpes

zoster by decreasing lymphocyte counts.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I have two questions, one on efficacy and one on safety. For Dr. Jimenez on the efficacy one, we're being asked, again, about the effect of 10 milligrams versus 5 milligrams long term, and I was thinking that maybe some helpful data for us is to look at the open-label data. And on your study design, you show that the open label, there's a 5-milligram arm and there's a 10-milligram arm, and the 5-milligram arm according to the briefing document, there are 175 patients in that arm.

What I want to know is in the patients who got on the 5 milligrams from the maintenance, some of them who are on 10 milligrams BID or 5 milligrams, how did they do from an efficacy standpoint -- if you have that data -- in the open-label arm? Like for example, did the 10-milligram patients not do as well when they got to the 5 milligrams in the open label? That's my efficacy question, and I wish someone could show

that data if it's available.

My safety question is the patients on the 10 milligrams with more side effects or these adverse events, they're the more severe patients, they had been on prior TNF and that would probably contribute. I was wondering how confident the FDA feels that the drug really contributed to the higher safety or adverse events rather than it being, really, multiple contributing factors that could be due to just having a very severe disease and then also being on prior TNF.

DR. HANES: That is the crux of the question for today, so I'm glad that you asked that question. We are not a hundred percent confident at all, and that's why we're asking for your advice because there are so many confounders in terms of the design of the study, the limitations that we pointed out, the severity of disease between both dose groups. So we want your help and your guidance in terms of trying to decipher that.

What we do have is some information from the larger RA program and what's already in the

labeling, and then we've seen signals in the UC program, which are smaller. So that just leads us to additional questions regarding safety of how safe is the higher dose because it hasn't been approved, although it's been studied, but it hasn't been approved yet. So that is the question.

DR. CHANG: But in these other populations with more severe disease, do they have more of these adverse events, like RA or the psoriatic arthritis?

DR. HANES: It looks like the data has changed over time. I'd rather have the sponsor ask that because their newer data has shown different risk profiles.

DR. CHANG: Do you have the efficacy on the open-label 5-milligram arm?

DR. JIMENEZ: Could you restate that, please?

DR. CHANG: I think some potentially helpful information for us to look at the 5 milligram versus 10 milligrams more long term is we have the open-label 5-milligram arm. We have 10 milligrams.

We don't have placebo, but we do have 5 milligrams, and I'd like to know if the patients on 10 and 5 on maintenance who went to 5 milligrams on an open label, how did they do from the efficacy standpoint?

For example, if someone's on 10 milligrams, they're in clinical remission, they go into open label, they're on 5 milligrams, did they do worse because they went on the lower dose or did they just do as well?

DR. GRIEBEL: I think you asked that question earlier of the applicant, and I think what I'm seeing from the team, they don't have a slide to present on that. I don't know if the applicant wants to address this question again because it's still clearly an issue.

DR. SU: We do have data that show actually -- if we can have slide EF-7 up, I can give you more details that hopefully will address your question. This shows the results of the efficacy of what happens when patients go down to 5 milligrams in the long-term extension after being

on either 10-milligram maintenance or 5-milligram maintenance and are in remission at the end of maintenance study. And the data are obviously not controlled comparisons; the results were similar.

DR. CHANG: I'm sorry. So you're basically saying that if you're on 10, you don't do that much worse going on 5? It looks like you're -- the same.

DR. SU: These were patients who were in remission after one year of either 10 milligrams of maintenance or 5 milligrams of maintenance and what happens when they go to the long-term extension receiving open-label 5 milligrams. What we do not have -- and we recognize that's a limitation. We do not have direct comparison of taking patients who are in remission after 10-milligram maintenance and comparing them continuing on 10 milligrams versus going down to 5 milligrams, and we are working on exploring that question with the phase 3B study.

We actually do have some additional information that may help address the question

related to the 10 versus 5 for the maintenance -- the TNF treatment failure patients.

DR. SANDBORN: Dr. Chang, this is really a critical point. I think it would be worth stepping back just to comment on Dr. Jimenez's presentation because she made the point that there wasn't a statistically significant difference between the 5- and the 10-milligram group in the anti-TNF failure patients during induction, and we made the point that there was a nominally significant p-value, so 0.07 versus 0.04.

So what's the discrepancy? The discrepancy has to do with the analysis population. This is the only trial in history that I'm aware of where we needed a rerandomized maintenance trial. The sponsor was required to rerandomize the placebo responding patients into the maintenance trial and include them in the full analysis set. The only time that's been done before was Tysabri in Crohn's disease, but the primary analysis set was only in the patients who responded to Tysabri.

When we did that, we rerandomized into

separate strata the patients who responded to placebo, and they had a treatment effect, but it was much smaller. So if you're a placebo responder, you had a mild subsequent disease course, and the difference between drug and placebo responders was a lot smaller than the difference between drug and placebo in Tysabri responders. And again, in that program, the primary analysis for maintenance was only in the Tysabri responders.

Here we have I think a dilution of the treatment effect by including placebo responders into the full analysis set. And if you use the modified analysis set, which I would argue is more relevant here, then the nominal p-value for 5 versus 10 is significant. And again, the difference between 5 and placebo is not significant.

So now how to fit this in, because I think Dr. Chang has just nailed this, if you get out to a year and you're in remission on 10 milligrams -- and we could call this kind of deep remission. They've got endoscopic remission,

they've got clinical remission, and a really robust measure of clinical remission. And they're off steroids, and they would have been off steroids for a long time. So in that patient population when you get out to a year, if you drop down to 5, these data say that it looks okay.

Now, the one caveat to that is we don't see a stratified analysis of this for anti-TNF naive and anti-TNF failure patients. This is a mixed population, but still the overall numbers are so good that the failure patients must be pretty good. But to take these encouraging data about what happens in a year in the subset of patients who achieved deep remission and extrapolate it back to what to do with the end of 8 or 16 weeks of induction, where the results are very clearly different over the next year, I just don't think it's right. And to legislate to physicians that they may not use 10 milligrams for up to a year in that patient population because of these late data is not the right place from a clinical perspective in my opinion.

DR. RAUFMAN: WE have time for two more questions. Dr. Lebwohl?

DR. LEBWOHL: I want to ask Dr. Hanes and possibly the sponsor about cardiovascular events, particularly in light of the effect of tofacitinib on LDL levels, as we're facing the prospect of having patients take the 10-milligram dose in the long term. Long-term study results outside of UC are still pending, but within UC, we have a handful of patients who had events, and we were told that these patients had multiple cardiovascular risk factors.

Do we know if these subjects had a rise in their LDL, and do we think that tofacitinib mediated these events that way?

DR. HANES: That's a great question. In particular for LDL, I am not sure. Perhaps the sponsor might have -- but the risk factors that some of the patients had did include hypercholesterolemia. There was hyperlipidemia in the second patient, hypercholesterolemia in the third. So the breakdown of that lipid elevation

I'm not clear.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: Jenifer Lightdale. Just a clarifying question on the safety data. At slide number 61, you say large numbers of patients discontinued treatment in both groups. Is this the issue that was brought up, that patients were considered discontinued if they had to use steroids for a flare?

DR. HANES: It appears that multiple patients discontinued due to lack of efficacy. There was a small proportion of patients who discontinued, very small, for other adverse events, but most of it looked like it was insufficient clinical response, ICR.

DR. ALTEPETER: And I would just add that that's not necessarily different compared to other development programs. It's a limitation that we face with all of these drugs to date, but it does make it hard to know what might have happened to some of those people over time.

DR. VALDEZ: Hernan Valdez, Pfizer. The

sponsor wanted to ask some information that we have in another population, in a related population at heightened risk of developing cardiovascular event. That is the patients with rheumatoid arthritis. In this population of patients, we have studied the incidence of MACE, and we have performed several analyses that suggest that the increase in lipids are not associated with tofacitinib, are not associated with a heightened risk of MACE.

So among all the patients who participated in the tofacitinib development program, we first analyzed the patients who developed major adverse cardiovascular events, and we asked what are the risk factors that are associated with a heightened risk of MACE at baseline. We found, not surprisingly, that age, history of hypertension, and the total cholesterol to LDL ratio were associated with an increased risk of MACE.

Then we asked what happens if you exclude the initial follow-up and you count the MACE events after the first 24 weeks when we have already seen the increase in lipids? And after that analyses,

we found that actually the increase in LDL among patients who received tofacitinib was not associated with an increased risk of MACE. We recognized that these analyses are limited, the relatively short follow-up vis a vis the time that one needs to have hyperlipidemia to develop MACE.

So we have also compared the rate of MACE in the rate programs using established cohorts with one cohort in the United States and 4 cohorts in Europe. And we have found out that the standard incidence of a rate of MACE among tofacitinib recipients is similar to patients who are receiving TNF [indiscernible]. These data are not definitive, and that is why we will have the definitive data with the 1133 study.

DR. RAUFMAN: Dr. Altepeter?

DR. ALTEPETER: Thanks. If we could go back for a moment to Dr. Chang's prior question. I don't know that we completely answered you in regards to whether or not we're seeing these concerns about dose-dependent safety based on disease severity rather than just on the dose, and

I'm sorry we don't have slides for all of these things. But if you look in the background document, you see in table 27 and also table 29 that we did look at some of these adverse events of interest in the TNF blocker failure population. I think we could say -- although this is not stratified by Mayo score or things like that -- that in general we understand that this is a more severely affected population.

Interestingly if you look there, you don't necessarily see the dose-dependence. I'm referring to the rates of serious infection in the program overall for 10 versus 5 looked comparable within the TNF blocker failure subpopulation. And then similarly for herpes zoster, if you look at the predominant dose, 10 versus 5, you don't see the higher rate in those who got 10 versus 5 in that TNF blocker failure subpopulation.

So I think there is uncertainty depending on which analysis group you look at and which population, but certainly I think acknowledging that severity of disease affect some of these risks

is important, so I thank you for raising that point.

DR. RAUFMAN: We will now take a 45-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 1:15 p.m. Thank you.

(Whereupon, at 12:28 p.m., a lunch recess was taken.)

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

(1:17 p.m.)

DR. RAUFMAN: Before the open public hearing starts, we'll give the opportunity for the sponsor to just give a brief presentation, a brief clarification of one point.

DR. SU: We just want to take an opportunity to clarify some of the discrepancies of the data that you saw between FDA's presentation and our presentation, and they're two topics. The first one is related to the malignancy data, and I'll ask Dr. Schein to come to the lectern, and the second one is about the extended 16-week induction data, and we'll have Dr. Sands followed by Dr. Sandborn.

DR. SCHEIN: Good afternoon. I'm Phil Schein. I'm a medical oncologist/pharmacologist, former chairman of the Oncologic Drug Advisory Committee, but that goes back quite a few years. I'm here as a consultant to Pfizer, and they are compensating me for my time today.

I wonder if it would be possible to show the FDA slides, the slides that were just presented.

Would that be acceptable?

(FDA members nod yes.)

DR. SCHEIN: Oh, great. Can I have slide 67? And I'm not up here to disagree with anything that was presented. I think it would just be useful to perhaps provide the perspective of an oncologist in terms of how to interpret this data. And I'm bridging off a question that Dr. Chang raised earlier that I didn't think was fully responded to.

You raised the issue of the nature of the cases that are being rolled into these trials, and obviously they're pretty late. These are patients who have gone through other options where this represents perhaps the cohort of the last resort. In many cases, they've had decades of active ulcerative colitis, they've had steroids, and they've had thiopurine therapy. And you can see from this slide, 92 percent in the FDA's estimate, and 77 percent have had prior TNF blockers.

So they're coming late, and there's a lot of baggage they've accumulated over those years, so it

does make it very difficult to interpret these cases. And I will put this in the context of what we know about cancer. It's the second leading cause of death in the United States, an extremely prevalent disease.

A database of this size, if it did not have cancer cases, would be I would estimate rather unusual. So cancer is to be expected simply with following these cases over time. So the real issue is, is this drug contributing to anything that arose, and that is obviously the challenge for all of us today.

Could I have the next slide, please? I think the FDA did a marvelous job of presenting these cases in a capsule form, but let me just highlight a few of them based upon my review of these cases. And I've gone through each of them as thoroughly as I could based on the data that was available.

Now, the gastroenterologists would know that cancer of the colon doesn't rise very quickly, but the cancer societies' guidelines for colonoscopy is

every 10 years. There's a reason for that period of time; perhaps a little shorter if you have some risk factors, but it's years.

As was previously presented, in the case of colon cancer arising in the setting of active ulcerative colitis, you're talking about decades, two and three 3 decades. It's a late disease. So we can say that generally for solid tumors, they don't arise in a year. A very conservative estimate would take at least four years from the initial mutation, but more likely a decade. You can go to almost any carcinogen and derive that data, and particularly the most common one, cigarette smoking asbestos, it is decades.

So let us look at one or two of these cases. I'm not going to go through them completely, but just to put this database into perspective so you have a feel for how much solid information you can derive from the mention of a cancer case to the actual possible implication of a drug and its causation.

Let me take the very last case,

adenocarcinoma of the colon, cumulative days on treatment, 50. That would not only be a new Guinness book of records; that would be absolutely biologically implausible. Nevertheless, it's on the list. It's counted as one of the 15 or 14, depending on the dose, and there are other cases like this in there.

The Epstein-Barr virus case, that's a patient that had a couple of decades of active ulcerative colitis, and as shown here had prior therapies, a lot of thiopurine and the additional use of TNF blockers. Approximately 3 months after entrance in the study, the patient has a lymphoma. What was the contribution of this therapy for a tumor that arose so quickly or was it latently there and growing at the time of study entry?

Can I have the next slide, please? There may be a coding error here, but this case of a central thrombocythemia, when I looked at the data, the platelet count at time of study entry was 759,000. It remained at that level stable through several years of the treatment. But this patient

entered with that problem. It was subsequently diagnosed while the patient was on study. But again, counting it as a case in which this drug may have contributed it I think might be unreasonable in that setting.

The lung cancer case at the top had 33 years of cigarette smoking. I'm not saying that you dismiss any of these cases from your thinking, but just to present it in a table, whole, without some interpretation makes it rather risky.

Can I have the next slide, please? The FDA showed this curve. It's truncated in terms of how far it goes up, 1.5 percent in terms of cumulative incidence, and you can see the study time. This is for 10 milligrams. With the two new cases that have just been registered in the last couple of months on 5 milligrams, there are now three cases in this series at 5 milligrams with a denominator of 200; that's 1.5 percent.

I'm not suggesting you accept that the numbers are entirely too small, but I think that's what we're dealing with here, is very small

numbers. So to look at individual cases without looking at the picture again could create some risk.

DR. RAUFMAN: Thank you. We're going to have to --

DR. SCHEIN: One more slide, please, Mr. Chairman, and then I'm done. This will be quick.

DR. RAUFMAN: We really need to move forward.

DR. SCHEIN: Okay. Can I just have SA-33, and then I'll leave. I promise. SA-33, please.

DR. RAUFMAN: No. We're going to have to move on.

DR. SCHEIN: Okay.

DR. RAUFMAN: Thank you.

DR. SCHEIN: All right.

Open Public Hearing

DR. RAUFMAN: Both the Food and Drug Administration, 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, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency

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

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

MR. CAMPBELL: My name is Guy Campbell. I did have some initial contact with Pfizer to determine the logistics of attending this hearing, but I do not represent them, and I'm not being compensated by anyone, and I'm here strictly as a former ulcerative colitis patient.

I was diagnosed with moderate to severe ulcerative colitis in 2011. For two years, the

disease was kept under control using Canasa and Asacol HD. Then the dam broke in October 2013, and the disease careened out of control and became very, very severe. And for 14 months, I went through azathioprine, Humira, Entyvio, Remicade, and methotrexate. None of them were at all effective.

In between trying these drugs, I had to go on prednisone, theoretically on a temporary basis, to calm things down, but I eventually became prednisone dependent. Nothing worked other than prednisone. At the end of 2014, I changed gastroenterologists and proceeded again to go through many of the same drugs under the theory that maybe something was missed the first time around, and as of 2015, I conceded the disease had one, and in October 2015, I had an ileostomy.

Much attention is focused on the medical and physical damage to the body that ulcerative colitis can cause improperly so, but less seems to be discussed about the emotional aspects of the disease. Severe ulcerative colitis sucks the life,

vitality, strength, and self-confidence from a person. Job performance can very much be negatively affected. Severe ulcerative colitis can also be a disease of desperation for some patients. Crazy diets, meditation, supplements, and other forms of hoped for holistic cures are tried by frustrated patients seeking to do anything to save their colon.

Then there is the impact on the family. A person struggling with severe ulcerative colitis is very difficult to live with. The disease can complicate the patient's relationship with children. My children happen to be well into their adulthood, but my grandchildren used to call me Grumpy Grandpa. The disease places significant stress on a marriage, and I think more attention should be given to the effects of this disease on a spouse.

In short, ladies and gentlemen, struggling with severe ulcerative colitis is not for the sissies. Life becomes much more difficult if you are struggling with the disease, which brings me to

why I'm here. My pitch is that current and future severe ulcerative colitis patients surely need a new drug that hopefully is effective for them. It would be nice if Xeljanz is that drug since it seems ahead of the competition in terms of the development pipeline, and it's also available currently as the treatment for another disease as I know you all know.

Xeljanz has the additional advantage in that it is a pill; no more injections, no more 2-hour infusions. I do not mean to imply that a new drug should be approved outside of a disciplined approval process that takes into account the potential risks, however, I do hope that the risks will be considered on a relative basis. By that I mean surgery is increasingly becoming the only option for patients that have no effective drug to turn to, and surgery has its own group of risks.

So the longer these people do not have a drug to turn to for relief, the more these people will assume the surgical risk by default. Thank you.

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

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin, and I'm a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, policymakers, and providers. We do not accept funding from the drug or medical device industry, so I have no conflicts of interest.

Patients with moderately to severely active ulcerative colitis need safe and effective treatments to help them better manage the disease. The goal is to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer.

We are glad that the FDA and the sponsor are working together to try to determine whether this drug is an effective and safe treatment for

patients with ulcerative colitis. We agree with the FDA's scientific assessment that there are concerns regarding this drug's efficacy and safety for some dosing regimens and patient subpopulations. I will highlight our major concerns.

First, we are concerned that the sponsor's proposed dosing regimens of focus are based on exploratory analyses. For patients without adequate therapeutic response at 8 weeks and for those with a history of prior failure with a tumor necrosis factor blocker, the sponsor proposed special dosing regimens, however, the sponsor did not use multiplicity controls, which are tools that prevent scientists from incorrectly stating that they have evidence that a drug works when it actually does not. Exploratory results cannot be relied upon to adequately support the sponsor's proposed dosing regimens. The sponsor should be required to provide data ensuring that these proposed regimens are safe and effective before supplemental approval.

We are also concerned that the sponsor's studies include too few African American patients. As the FDA noted, less than 1 percent of participants in the overall safety analyses were black, and only 2 black patients were treated in the maintenance trial.

In contrast, 1 in 4 patients at large treatment centers are black. In addition to be disproportionately low, there were too few black patients to have any confidence that this drug would be safe or effective for this subgroup. We strongly urge the FDA to delay a decision about approval until the sponsor conducts studies in representative patient populations who face significant disease burdens.

In summary, we are concerned that the clinical trial data do not adequately represent the real-world population of patients who will be likely to consider this drug. In addition, inadequate data prevent us from knowing whether the 10-milligram BID dose will be safe or effective for patients who do not achieve adequate therapeutic

benefit after 8 weeks of that dose. The same is true for the 10-milligram BID dosing as continuous maintenance treatment for the subgroup of patients who have previously failed with the TNF blocker.

Based on these concerns, we strongly recommend more persuasive data, including a more diverse group of patients before making a decision about supplemental approval of the two proposed dosing regimens for induction nonresponders and those with prior TNF blocker failure. Thank you for the opportunity to share our perspective with you.

DR. RAUFMAN: Thank you. 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?

MS. MORGAN: Good afternoon. My name is Emily Morgan, and I'm an ulcerative colitis patient representing myself. I want to first thank you for the opportunity to participate in the open public hearing today. I appreciate your time and willingness to hear from patients and family

members, researchers, and foundation members like myself. There are limited treatment options available for ulcerative colitis. It's important when new therapies are developed, and I strongly encourage the committee to support approval of these new therapies that meet the FDA's standards for safety and efficacy.

As you may know, treating UC requires an individualized approach. Not only are all patients' disease course different, but treatment options for ulcerative colitis are limited compared to those available for Crohn's disease.

In addition, not all available drug treatments for ulcerative colitis work for each patient. There are only three years from the time I was diagnosed with colitis to the point where I had tried every available drug for the disease and failed. The only thing keeping me from clearing [indiscernible] was prednisone, and that was no way for a 15-year-old to live. No teenager, nor anyone for that matter, should have to suffer the brutal effects of long-term steroid use.

I was unable to participate in the same activities as my peers, but I also began to question my purpose. I wondered why me. I alienated myself from friends, family, and everyone who was trying to support me. Ulcerative colitis controlled my every day. Nothing worked. My family even sought a second opinion, and still nothing was working.

High school is a blur. I have very little memory of anything other than doctors' visits, hospitalizations, and my own bedroom. My reality was a nightmare. I was only left with one more option, surgery. When I was 16 years old, I had my entire colon removed. There were two operations, and I had a temporary ostomy for 2 months. Fortunately for me, surgery has really saved my life. I have been able to enjoy a somewhat normal life despite my disease ever since, but that's not the case for every patient.

The Crohn's and Colitis Foundation estimates that 25 to 33 percent of ulcerative colitis patients will require a colectomy. This number has

improved thanks to treatment advances and changes in the disease management. Considering both these numbers, as well as looking back at the rollercoaster of a time I endured prior to surgery, it's absolutely critical that we continue to strive for more therapies available to patients and ultimately a cure for ulcerative colitis.

Thank you so much for providing me with this opportunity to share my story. I encourage the committee to support the approval of new treatments for ulcerative colitis patients that meet the FDA's safety and efficacy standards. Thank you.

DR. RAUFMAN: 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.

MS. WINGATE: Thank you. My name is Laura Wingate, and I'm the senior vice president for education, support, and advocacy for the Crohn's and Colitis Foundation. I am here representing the foundation and I have no financial conflicts.

Thank you to the members of the FDA's

Gastrointestinal Drug Advisory Committee for the leadership, time, and opportunity to address this panel. The mission of the foundation is to cure Crohn's disease and ulcerative colitis and improve the lives of children and adults affected by these diseases. As you may know, the foundation supports basic and clinical research at the highest quality, offering a wide range of education programs for patients and healthcare professionals while providing support and advocacy for those living with ulcerative colitis.

Within our education, support, and advocacy department, we offer an IBD Help Center, which provides disease-specific information to support the 1.6 million Americans living with Crohn's disease and ulcerative colitis. The IBD Help Center over the last 10 years annually fields 11,000 calls and emails from patients and caregivers. The most frequent questions related to these calls are that patients are seeking information on the treatment for their inflammatory bowel disease.

For many patients, there's a lack of an effective treatment as you've heard from the prior speakers. Patients often experience a delay in diagnosis, and finding an effective treatment can take years, leading to worsening symptoms, loss time from work and school, and in some cases, disability.

The most difficult questions the foundation receives are from those patients who have tried and failed every available treatment, as you've heard from the prior speakers. These patients are suffering and struggling to find a treatment that will allow them to engage in everyday activities, including work, going to school, and engaging with friends and family. Therefore, it is vital to work to provide as many treatment options as possible for these patients.

The foundation encourages the FDA to support the approval of any appropriate and efficacious treatment that meets the FDA's strict standards. Thank you to the FDA's Gastrointestinal Drugs Advisory Committee for allowing me to address this

panel.

Questions to the Committee and Discussion

DR. RAUFMAN: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I will read the questions as we go along. Question 1 for discussion, the applicant has proposed an induction dosing regimen of 10 milligrams BID for a total of 16 weeks in patients who have not achieved adequate therapeutic benefit by week 8 based on exploratory analyses of trial data in patients who continued induction

treatment when they had not achieved clinical response defined as a decrease from baseline in Mayo score of greater than or equal to 3 points and greater than or equal to 30 percent with an accompanying decrease in the subscore of rectal bleeding of greater than or equal to 1 point or absolute subscore for rectal bleeding of zero or 1.

A. Please discuss the adequacy of the efficacy data to support the use of the 10-milligram BID dosing for extended induction therapy for a total of 16 weeks in patients who have not achieved adequate therapeutic benefit by week 8.

B. Please discuss the adequacy of the safety data to support the use of the 10-milligram BID dosing for induction for a total of 16 weeks in patients who have not achieved adequate therapeutic benefit by week 8.

Are there any questions or comments concerning the wording of the question?

(No response.)

DR. RAUFMAN: If there are no questions or comments concerning the wording of the question, we

will now open the question to discussion.

DR. PARDI: I can go. To me, one of the biggest questions here is the word "adequacy." As we heard from our statistical advisors and from some speakers, this was not placebo-controlled data, so it's observational data. Having said that, 50 percent of the patients responded to an additional 8 weeks of therapy, and I didn't see much in the way of a safety signal. So in my opinion, the balance of efficacy versus safety seems to be in favor of this indication.

DR. RAUFMAN: Dr. Fuss?

DR. FUSS: In slide 43 that the FDA showed, this was looking at the timing -- sorry. So if you look at this at month 2, month 12, month 24, looking at and seeing an increased efficacy rate, again, not placebo controlled, we don't know that placebo rate. These biologics essentially don't just work, and usually don't work, just by neutralizing the type of cytokine. They work usually by knocking out the types of cells that generate the inflammation. In a lot of the

biologics, they work by apoptosis or cell death or inducing the cell death.

In this case, this type of drug, although the primary mode of action still remains under examination, primarily it works by stopping or decreasing the generation of these inflammatory cells that cause the inflammation, not just by blocking the inflammatory pathways.

So what I'm getting at is the reason you're seeing this lag and it's taking time, it's taking time to knock out those cells and knock out the generation of the cells. So the longer you give it, the more efficacy you should start seeing is what I'm seeing in this panel. And at least, I agree with Dr. Pardi, within that, say, 8 weeks or 2-month extension, the safety period looks pretty good still, and you're getting some increase in efficacy that probably primes you to then go into the maintenance phase to get a better efficacy at a 5-mg dose.

So I would concur that at least by a mechanistic standpoint, an additional 8 weeks in

the nonresponders who probably have more difficulty knocking out those cells, you need those additional 8 weeks.

DR. RAUFMAN: Dr. Grayson?

DR. GRAYSON: I agree with everything that's been said. I just want to point out that this is definitely in Caucasians. And the lack of diversity is concerning, as pointed out by the agency and actually one of our public speakers as well. I don't know how that weighs in on answering the question necessarily, but I think it's something we need to be aware of.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: I guess after the discussion started, I guess I do have a question about the question itself because it says please discuss the adequacy of the efficacy data and support the use of the 10-milligram for extended induction therapy for a total of 16 weeks, in comparison to what? In comparison to not giving them anything or in comparison to giving them 5 milligrams? Because those two are very different, and I don't think we

have good evidence at all about the comparison with giving them 5 milligrams versus 10 milligrams. So I guess it depends on what we're comparing it to.

DR. RAUFMAN: Could we get clarification from FDA on that?

DR. GRIEBEL: I guess the clarification would be it is what it is. Based on the data that we have for this particular situation, which is 16 [sic - 10 milligrams] milligrams, when you have not achieved response at 8 weeks, you go on for additional 16 weeks uncontrolled. I think you may have pointed that out in your discussion. We're asking you to comment on the adequacy of the efficacy data because it is uncontrolled. You can make comparisons, but you don't have a prespecified group.

DR. PROSCHAN: Right. I see those as very different. I think I probably concur that the 50 percent response for people who initially didn't respond is probably more than you would expect by regression of the mean and more than you would expect if you gave placebo. I don't know at all

whether it's more than what you'd expect if you gave 5 milligrams though.

DR. RAUFMAN: Dr. Pardi?

DR. PARDI: Yes, I agree with that. It would be interesting from a scientific perspective to have a 5-milligram arm, and maybe you just needed a longer therapy on some dose to see the benefit. I'm less concerned about that given the safety profile of the 10-milligram dose though.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I don't think the question was asking about comparing the dose. I think they're just asking in patients who did not reach a clinical response for 10 milligrams versus placebo, if you extended it for another 8 weeks, if you would have an adequate clinical response. And I feel like the data shows that it does because 50 percent of people who would normally probably would have been dropped, they actually responded.

I think your point, Darrell, that it wasn't placebo controlled, I think the good thing that at least I feel comfortable about is that the initial

8 weeks was placebo controlled, so you would have gotten rid of placebo responders. They wouldn't have responded, right? I mean, there could still be some placebo response in the following 8 weeks, but I don't feel as worried about that.

DR. RAUFMAN: Dr. Lebwohl?

DR. LEBWOHL: To that end, I do think there is a possibility for a new boost placebo response once people know that they're gone open label. And I guess my question about adequacy of the evidence -- and perhaps we can ask our colleagues at the FDA who have the institutional memory, how unprecedented would it be for us to grant this kind of recommendation for the 16 weeks in the context of no placebo arm for those second 8 weeks? Is there precedent in prior drug approvals for that kind of decision?

DR. GRIEBEL: I cannot think of a precedent for saying continue to treat and see if you get a response. We generally label based on how the trial was designed and where we have the evidence. I can think of precedence similar to this case,

where you have efficacy; you've established efficacy at two dose levels where both doses got approved and the clinician was left to make the decision. The issue here is what are our questions about safety attached to each one of those doses.

DR. CHANG: I did have one other thing that I wanted to bring up, the whole thing about lack of study in African Americans. I guess my question is, is there any data in a UC population that there are racial differences with response to treatment? I know this is a novel mechanism, so I'd want to know that.

Second, with the other patient populations that have had this drug, is there any evidence that there's a racial effect on response, efficacy, and on safety?

DR. HANES: I can provide a partial answer to that. Based on the literature that I reviewed, it appears that African Americans or perhaps black patients might have a more severe course of disease particularly when they're diagnosed and when they're treated. So I think that has to be

accounted for when looking at drug evaluation.

What else did you --

DR. CHANG: Is there any data on the efficacy and safety of this particular drug in the larger patient population, rheumatoid arthritis, psoriatic arthritis? Is there any difference in their efficacy or safety; if you have more data on a more diverse racial population?

DR. GRIEBEL: We're going to defer to the applicant.

DR. SU: First, we acknowledge that we do have a small number of patients for Afro Americans in the UC program. From the larger RA program, not a lot of our sample size, but we did not see a difference for that matter. In terms of precedence, what I will ask Dr. Sandborn to comment on is our understanding of vedolizumab approval, dosing recommendation.

DR. SANDBORN: Dr. Griebel, maybe you and I can remember together. I'm trying to remember if I got this right. But with vedolizumab, I think the way it worked in ulcerative colitis was that

patients got dosed to zero in 2 weeks and then they had a primary assessment at week 6, and the responding patients were rerandomized to every 4-week or every 8-week dosing out to a year. And yet, the label reads that patients could continue through week 14 before a decision is made as to whether they failed the drug or not.

So my interpretation of those data are that it did allow for late responders despite the lack of control trial evidence between week 6 and week 14, if I'm remembering that correctly.

DR. GRIEBEL: Right. I was surprised when you brought that up -- it might have been Dr. Sandborn that brought it up in the presentation. I didn't remember it that way, and I was over here scrolling looking at the label and looking at the trial design, and I think what -- I don't want to go into the details, but I don't think that my conclusion would be the same as yours if that's where we -- that there was a differential based on a different approach to dosing.

I think that the primary efficacy evaluation

was done at whatever week is the last dose given in induction and that the label states that the last dose is given on that date, and then you reevaluate and make a decision about further dosing if it gets like 8 weeks later. But I'd have to go back and look at the review. I may be misrepresenting.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I'll just note, just thinking clinically, when you see patients start to respond to whatever treatment you're treating them with, often they start to tell you that they're feeling better before, of course, you'll see mucosal healing. They start to tell you they're feeling better before lots of things happen. So you can try to break it down for them, but are they waking up in the middle of the night to go to the bathroom? How many times are they stooling? Are they able to just feel better so they move around? And that's all happening before they finally get there.

It's interesting to listen to you, Ivan, because I'm like, okay, that explains this sort of

flow expression, I think, of what's happening, probably. But I think this concept that you're going to get exactly to what you want to get to by week 8 is so artificial on our part, that we have to respect that this disease is tricky, and you've got to give people time to respond, if that helps, how I'm thinking about this. I think the safety, yes, it's obviously a little bit more worrisome for 10 milligrams BID, but it's in the end not that much different. You're still having those discussions with the patients, and they're still hoping the drug will work.

DR. RAUFMAN: I'm hearing in general not much concern about part B, about the safety data. Is that what I'm hearing from the members of the panel?

DR. LIGHTDALE: I would say yes.

DR. RAUFMAN: Regarding the paucity of African Americans in the studies and so on, is that concern sufficient to deny the drug to the 75 percent of patients who are Caucasian or other ethnicities? How much of a concern is that? Dr.

Grayson?

DR. GRAYSON: I raised it more just to say it. I don't actually think -- in my mind, it's not a reason to withhold the drug from the other 75 percent; it's just an unfortunate occurrence in the studies. It would be nice to know what happens going forward. But I don't think there's anything to suggest that the drug would act differently in African Americans or that there would be other safety effects with it. I think it's a big problem, but I just wanted to make sure we were aware of it.

DR. ALTEPETER: Following along on those lines, could we ask the sponsor to describe any other differences in safety that might have been noted by racial groups, and in particular share data about herpes zoster in the Asian subpopulation for example?

DR. SU: Yes. As you pointed out, we do see a high rate of herpes zoster in patients from Asian countries. It's probably most useful to look at the large RA data, and I'll ask Dr. Valdez to show

you those data.

DR. VALDEZ: Hernan Valdez, Pfizer clinical. We have examined the rate of safety events by race, and if we look at the larger clinical trial programs like rheumatoid arthritis and psoriasis, there is actually no higher safety there than in African American patients or patients with African descent.

We have noticed the increased rates of herpes zoster in Asian patients, and we have tried extensively to find out the rationale why patients of Asian race have an increased rate of herpes zoster, and looking at pharmacokinetics, that was not the answer. We have genotypes to do whole genome analyses of the whole trial population across indications. We have found a couple of hits that we're following on, but that is related to the Asian population. In the African American population, we did not see any safety difference relative to the population as a whole.

DR. RAUFMAN: Dr. Strate, did you have a question?

DR. STRATE: This is just more of a logistical question for a person's first time on the committee. And it sounds like from the nature of the questions, this is true. Should we approve this, does that restrict in any way recommending future studies about dose or diversity of the patient population?

DR. RAUFMAN: I think the answer is no, it doesn't. Is that correct? Yes.

Other comments?

DR. STRATE: One more comment. When we're looking at these patients, I think we have to take into our thinking that these are patients who have failed a lot of other therapies and who have few other options. So as a clinician, I'd be thinking about this, do I want to extend this 8 more weeks versus maybe no other options other than colectomy or adding additional therapies? I think that's how I'm thinking in my mind right now for the short term.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: Regarding safety, I think

with herpes zoster anyway, it does look like there's a dose response in terms of safety, and some of those cases sounded like they were pretty serious. I can't remember whether it was 4 or 6 that looked like they were very serious. So I think that's a concern for sure.

DR. RAUFMAN: Dr. Grayson?

DR. GRAYSON: What I was pointing out was that in the -- I don't know what slide number this is, but -- 82? In slide 82, if you look, there is a dose response, but actually in what would be the first 16 weeks, there's no real difference between the two doses. So in terms of what we're talking about for this question, there doesn't appear to be a dose issue. But then it does start to split off after that.

DR. PROSCHAN: Right. That presupposes that whatever risk is created goes away. I don't know that. I mean, it could have a long-term effect.

DR. RAUFMAN: I thought we were shown data that these cases resolved. I thought we saw a table of resolution.

DR. CHANG: The FDA also brought up in their document -- if you look at table 28 and 29 for herpes zoster -- that if you take the subgroup of patients -- and there's not a large number of them, but there is a subgroup of patients who are TNF blocker failures, which are typically more the severe patients; that there is no apparent dose-dependent increased risk of herpes zoster. That was getting back at the -- we were trying to talk about the risks. That's at least some indication that it may be that's not really a dose effect, at least that aspect.

DR. RAUFMAN: Dr. Jones?

DR. JONES: I don't think there's any question that zoster is an issue. I think we see it. There probably is a dose dependence, and there's probably some contribution from lymphopenia. What the question really is, is can we manage this risk? And I think now that we're going to have a zoster vaccine that can be given, we think, safely to folks who are on immunomodulatory therapy, I tend to worry a little

bit, maybe erroneously, but worry a little bit less about this.

In patients with rheumatoid arthritis, we have really tried to immunize people early, although that's complicated, and in the UC patient population who may be somewhat younger, even more complicated. But I think that when we think about these new vaccines, we should be putting that into mix here to say this may be a risk that we can manage even though I agree that it's there.

DR. RAUFMAN: Yes?

DR. ALTEPETER: Can I just offer -- we do have a backup slide that shows another way of looking at the safety of this second 8 weeks, and maybe that might be helpful to answer your specific question. It's the FDA backup slide number 6.

The data showed here, we asked the sponsor to take a look at what happens to people who are on treatment on the second 8 weeks of this 16 weeks, so it's sort of broken up. But if you compare the columns here, you can see the rates of herpes zoster.

The first column is describing patients who received 10 milligrams for the first 8 weeks responded, and then just by chance in rerandomization got 10 more weeks for a subsequent -- so they got at least 16 weeks of therapy, and what happened to them in that second 8 weeks of 10-milligram therapy, as opposed to these induction nonresponders who then got that second 8 weeks of active therapy, which is the fourth column there.

So again, these are small numbers, and I don't know for sure what you can say about it. But we did look at it in these different ways, and overall, our conclusion for the safety part was probably that we didn't see major difference in safety. I don't know if that helps.

DR. SU: Can we just add one clarification to one of the questions, at least to the difference between 5 and 10? We recognize the rates are different in the long-term, the maintenance therapy, but characteristic-wise, they are similar.

If I could just have slide SA-188 up, if you

look at our experience across tofacitinib development programs, when we compare not the rates but the characteristics, the severity of those herpes zoster events between 5 milligram and 10 milligram, they're actually rather similar in terms of the severity, how many cases are severe, how many cases are serious, and how many cases led to discontinuation.

DR. RAUFMAN: Thank you. Additional discussion?

(No response.)

DR. RAUFMAN: I'm going to try to summarize that discussion. In the aggregate it seems like in response to item A, there is generally support for the use of the 10 milligrams for a total of 16 weeks and limited concern about the adequacy of the safety data. Does anybody disagree with that summary?

(No response.)

DR. RAUFMAN: Let's move on then. Now we get to a voting question, and I'll read this. Do you recommend the inclusion of this dosing regimen

for this population in the product label? If you recommended inclusion of this dosing regimen in the product label, please discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy.

Do you recommend the inclusion of this dosing regimen for this population in the product label? If you recommended inclusion of this dosing regimen in the product label, please discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy?

Is there any further discussion at this point? Dr. Jonas?

DR. JONAS: Not discussion, but I just want to comment that we really don't have any data on A. Everybody who didn't respond in the induction went into the open-label extension at 10 milligrams. So

there was no decision point, unless I missed something here, about patients who would not go on if they were inadequate responders. So I'm not sure how we can answer A.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: I think this comes back to do you recommend inclusion of this versus not giving anything or versus some other option.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I actually heard it differently. I think the patients that you're talking about are those ones that they considered fell off the -- they basically didn't respond. So I think what I was hearing is then they needed more steroids essentially or whatever was going to try to rescue them. And at that point, they were discontinued from the trial. So we do have some data. We know large numbers of patients in both arms were discontinued.

DR. RAUFMAN: Dr. Fuss? The same question? Dr. Lebwohl?

DR. LEBWOHL: So if we know that about

50 percent of those who initially didn't respond in the first 8 weeks respond in the second 8 weeks, it would be helpful if we had some post hoc analysis of what were the predictors of those who responded in the second 8 weeks. I don't think we heard that from the sponsor. That might give actionable recommendations to clinicians.

DR. RAUFMAN: That question was asked. Someone asked about biomarkers and so on, and the answer we got was that there really wasn't much.

DR. SU: So as far as your question, we did try to look at those patients who responded to that actual 8 weeks versus those who did not, and we looked at the baseline demographics and characteristics. We did not find anything that's clinically relevant that really differs.

I think in terms of this question of what constitutes inadequate therapeutic benefit, our trial has a certain definition based on clinical response, and I would ask Dr. Sands if he could give that clinical perspective to help you make that recommendation.

DR. SANDS: Thank you. Bruce Sands. Mount Sinai, New York. I'm a consultant for Pfizer. I think permitting this dosing just sort of unties the hands of the physician to have a risk-benefit discussion with the patient. I think the common-sense thing is if the patient is actually showing signs of toxicity, if in their ulcerative colitis, they have fever, abdominal distension, things that are very worrisome, they're really deteriorating, then that probably takes the option off the table and should not even be offered.

On the other hand, if the patient is doing about as they had done when they came into the study and the patient expresses tolerance of that level of symptoms and they wish to go forward, I think that would be reasonable. So I think basically it's in the hands of the treating physician in a discussion with their patient.

DR. RAUFMAN: Any other discussion?

(No response.)

DR. RAUFMAN: If there's no further discussion on this question, we will now begin the

voting process. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing -- they're already flashing -- and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're 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. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to.

Any last questions/comments before we go to a vote?

Dr. Assis? Dr. Assis, are you there?

(No response.)

DR. RAUFMAN: Dr. Assis, are you there?

DR. ASSIS: Can you hear me?

DR. RAUFMAN: Yes.

DR. ASSIS: Okay. Sorry. Just to summarize, I agree that the data is [inaudible - interference], but I do concur with the concept, given an imperfect data set, that giving the best chance for a response and giving the potential 50 percent of patients a short-term continuation is reasonable, and those are my comments.

DR. RAUFMAN: Thank you. Any final comments? Everybody can go ahead and vote.

(Voting.)

DR. FAJICULAY: For the record, the results are 15 yes, zero no, and zero abstain.

DR. RAUFMAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. If we start from my right, I think Dr. Proschan, you're the first voting member on that side.

DR. PROSCHAN: Yes. I interpreted that as

do you recommend that versus not doing anything. I think the case is compelling enough to concludes that it would better than not giving them anything. I have absolutely no confidence that it's better than giving 5 milligrams. I don't know the answer to that, but I didn't interpret the question that way.

DR. RAUFMAN: Thank you. Please state your name before you tell us how you voted.

DR. PROSCHAN: Sorry. Michael Proschan.

DR. GRAYSON: Mitchell Grayson. I would agree. I voted yes. I don't know whether the 5 would have worked or not, but I think that there's evidence that the 10 did. Yes, it's an imperfect data set; yes, it has all kinds of problems, but I think still there's enough of a signal there with what I consider relatively minimal risk in the 16-week period, that I think it's worth it.

DR. FUSS: Ivan Fuss. I also voted yes for some of the reasons I mentioned as far as the efficacy of the drug and the timing of the drug, and less so on safety issues, at least during this

short time period. The only concern I would have is more addressed to Bruce Sands and others in that in the perfect world, yes, you can have a black or white where patients have fever, they need transfusions, they're losing blood, you know you're not going to continue it.

DR. RAUFMAN: You can be rude and face away. Just talk into the microphone.

DR. FUSS: My concern is for the patients more in the gray zone, I think there's going to need to be some more education to more of the GI community what constitutes inadequacy of therapy or when or what guidelines do we use to continue therapy for a 16-week period.

DR. JONAS: Beth Jonas. I voted yes. I think really the issue in this is clinical judgment, and I'm not sure that we can overlay our opinion about clinical judgment, but I agree that there's going to be a real education around this.

DR. LANE: Cliff Lane. I also voted yes. I think it obviously is a drug for which there's very clear demonstration of efficacy by a novel pathway

in a way that I think may have a substantial impact on the quality of life for the patients. I would add on the dosing question that I'm glad we weren't talking about 10 milligrams versus 20 milligrams of prednisone because I think that could have been a real challenge sorting out efficacy from toxicity.

I think what we have is we have a class of drug that has an effect on the immune system. And just like there's a trend perhaps towards efficacy at a higher dose and a trend towards more side effects at a higher dose, I think the challenge will be for the community of specialists to come up with guidelines that help physicians use the right dosing with the right schedule that is often beyond the ability of any single clinical trial.

MR. MATSON: I'm Tracy Matson, and I voted yes. We're talking about extremely ill patients running out of options, and I thought the risks versus rewards were certainly worthwhile to continue the therapy.

MS. McVEY HUGICK: This is Joy McVey Hugick, and I voted yes as well and piggybacking on what

everyone else has said. I think the one thing I would also add is that as important as it is to educate the clinician, I think educating the consumer is well would be important in this context as well.

DR. STRATE: I'm Lisa Strate. I guess I mirror what other people have said. I recognize the imperfections in the data. There did seem to be a signal. This is a desperate patient population. I think the risk is over a short term. And in clinical practice, we often escalate dose and IBD, so we're relatively used to doing this, but with a lot of insurance hassles. I guess I'd appreciate data going forward on risk stratification on ways that we can predict who might respond, and on dosing, whether 5 milligrams might be similar.

DR. PARDI: I'm Darrell Pardi. I voted yes for the reasons already stated.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes for the reasons that have already been stated.

DR. LEBWOHL: Ben Lebwohl. I voted yes for

the reasons that have already been stated.

DR. CHANG: Lin Chang. I voted yes. I definitely think there is greater benefit than risk, and I agree with Dr. Sands, what he said. My assumption is that when this drug comes out, for the refractory patients, they will be initially managed by IBD experts, and gathering their guidance and their experience will probably help guide other physicians moving forward.

DR. KHURANA: Sandeep Khurana. I voted yes.

DR. LIGHTDALE: Jenifer Lightdale. I voted yes for the reasons already stated.

DR. RAUFMAN: Dr. Assis, can you introduce yourself?

DR. ASSIS: David Assis. I voted yes for the already stated reasons, and I second the comment that I hope -- gathered post-approval on this respect.

DR. RAUFMAN: Thank you. We'll move on to the next discussion point. This is question 3 discussion. For adult patients with moderately to severe active ulcerative colitis with an inadequate

response, loss of response, or intolerance to TNF blocker therapy, A, please discuss the adequacy of the efficacy data to support the use of the 10-milligram BID dosing as continuous maintenance treatment; and B, please discuss the adequacy of the safety data to support the use of the 10-milligram BID dosing as continuous maintenance treatment.

Are there any questions or issues about the wording of this discussion question?

(No response.)

DR. RAUFMAN: If not, we will now open the question to discussion. Dr. Lebwohl?

DR. LEBWOHL: Though the lack of statistical interaction as noted, I think the effect size difference is impressive, and it mechanistically makes sense that patients who failed TNF blockade need a higher dose. So that to me is convincing that such a higher dose is indicated for that subpopulation.

DR. PARDI: Darrell Pardi. I agree with those comments. I think even if you use the data

set that showed that P equals 0.07, we have to interpret that in the context of the clinical benefit in this desperate patient population. For those who know the literature on other treatments for UC, the treatment effects seen here was very large.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I'm a little worried that we're using not responding to TNF blockers as a surrogate for severely enough active disease, and that's how we're now going to say that's how you get this 10 milligrams BID. In other words, I have kids who have severe IBD, and Remicade may not be their option; infliximab may not be their option, for lots of reasons, including these days, the insurance companies don't want to pay for it, which I actually think is a real issue.

The way this is written -- and I don't know if this is typical FDA discussion. The way this is written, this is going to lead to me having to put the child through infliximab first before using this drug. I don't know if we maybe right now

still do it. Because of selectivity, I'm comfortable with infliximab, know how to work with it, know what I'm expecting. But hopefully in a couple of years, an oral medication that doesn't disrupt everything, somebody stays home -- I mean, there are a lot of reasons not to set it up this way.

So I'm going to put that on the table. Is that okay?

DR. RAUFMAN: Dr. Jonas?

DR. JONAS: I also have a question about lumping patients who are intolerant of TNF inhibitors with the inadequate responders because that really marks something very different and doesn't necessarily portend a lack of response to the next medication.

So we see this all the time in rheumatic diseases, where the more biologics you've been on, the less likely you are to respond, but if you're intolerant and couldn't really demonstrate that the drug was not effective, then intolerance may be telling us something different than lack of

efficacy. But those people are lumped in terms of the way the trial was designed and the way we're thinking about it here. So I just throw that out there.

DR. SU: Can I just make one clarification? For the TNF treatment failure population, we do include primary, secondary, and intolerance, but intolerance patients is a small percentage. Pretty much the vast majority, well over 98 percent are either primary or secondary.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: You almost wish it read for adult patients with moderately to severely active UC, comma, such as those who had an inadequate -- it just needs to be a little bit looser.

DR. RAUFMAN: Dr. Assis, do you have a comment?

DR. ASSIS: I second the concern about adding to this particular question, because even though it was a percentage of patients in the trial, that could comprise a much larger number of

patients. And I would have a concern about placing them -- [inaudible - audio gap] about which we still potentially have safety concerns.

DR. RAUFMAN: Does one have to read this question as being limiting? It doesn't say for adult patients only. I don't know where you're going to put the "only." But I don't see it as limiting as you see it.

DR. LIGHTDALE: And you haven't negotiated with Blue Cross/Blue Shield recently.

(Laughter.)

DR. RAUFMAN: That happens to be true.

DR. ALTEPETER: If I may, I wanted to first address the comment you brought up about potentially not wanting everyone to have to have run through a TNF or something else like that. We try to put into the label a description of what the sponsor studied, and we don't necessarily require or recommend that they enroll only patients who may or may not have failed available therapies. This program at least included both people who fell into that group and also patients who may have failed a

more clinical conventional therapy.

Certainly the idea that you're raising -- and I think is one that's important for companies and investigators to think about going forward -- is do we always need to enroll patients who have failed something else because we never have that answer, which I think all of us who take care of these patients would like to know. Maybe the next drug is going to be better and should be your first-line agent, but we just have the limitation that we have to describe what their data showed. That was the first part of it.

The wording up here is, again, to do with how they define the population for which they are asking us to label the drug for this 10-milligram long-term use. And then I just wanted to offer, if you're interested, we do have the efficacy data broken down by primary nonresponse versus lots of response. That's small numbers, but if you want to see that, we can put that up there. That's backup slide number 16.

Obviously, the reason to look at this was

because we all understand that patients who have primary non-response to TNF may have a different pathway for their disease than those whose response is because of an inadequate trough, or development of antibodies, or things like that. Again, these are very, very small numbers -- note the N of 9 in the first tofacitinib group -- but this is the data that's available on that point, and this was for remission at the end of the maintenance trial.

DR. RAUFMAN: Dr. Grayson, did you have a comment?

DR. GRAYSON: I was just going to say that we really only saw efficacy, in my opinion, with the TNF failures. So the way this question is worded is very important to me because if you didn't have that in there, I would have a different answer. I like the way it's worded even though, potentially, you're right, it could be a problem with third-party payers. But I think the data support that, not the other way around.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: I actually think the data are

not convincing that the results are different in the two TNF failures or not. I'm reminded of there's a great book called The Treatment of Cancer, where Richard Peto has written one of the chapters. And he shows that if the overall effect has a p-value of about 0.05 and you have two subgroups that are the same size, it's not unusual at all for it to look like there's a big effect in one subgroup and not much going on in the other subgroup, even though the truth is exactly that, that it's equally effective in the two subgroups.

So I think it's easy to read more into this than is there. I consider this relatively weak evidence that there's a difference in response in those two subgroups.

DR. RAUFMAN: Again, I'm hearing no discussion about B, the adequacy of the safety data, so I'm interpreting that there's limited concern about that. Dr. Lebwohl?

DR. LEBWOHL: Yes, I think it's appropriate. If we can look at FDA slide 83, because that was potentially concerning, it looks like among those

with prior TNF failure, nearly 10 percent developed herpes zoster over the course of the 1-year period, and patients are potentially going to be taking this treatment longer. Now, perhaps the new zoster vaccine will be a game changer in that regard, and I really hope it is, but that's a number needed to harm of 10.

DR. PARDI: I'd follow that up by saying if I saw the data right, 95 percent of the cases of zoster were mild to moderate. So I was caught by that same number, been on that table, but when I look at that delta in risk compared to the delta in efficacy, I felt like the efficacy outweighed that risk, especially with a vaccine.

DR. RAUFMAN: Dr. Lane?

DR. LANE: Cliff Lane. I think it gets to a subsequent question, but again, the data we have is just for one year for a therapy that is anticipated to perhaps be for many, many years. So I think we have an adequate database in the short term but probably need to see one for the long term.

DR. RAUFMAN: If we could have the

discussion question back up? Any additional discussion here?

(No response.)

DR. RAUFMAN: So some different interpretations of how to read this and how limiting the wording is in terms of use of the drug. But still, again, I'm hearing a general consensus that even though the data have some flaws and some weaknesses, that overall they support the use of the 10-milligram BID dose, and we just heard that there's limited concern about the adequacy of the safety data.

MS. McVEY HUGICK: I just had a question, and it comes back to what Dr. Lightdale was talking about as far as coverage. I just want to make sure that the way this is worded, that patients won't have to run into that challenge about coverage through a third-party payer.

DR. PARDIO: I read this a little bit differently. This is not for the overall approval of the drug. This is for the approval of the extended 10-milligram dosing for another 8 weeks.

So this is saying in those who have failed TNF, we're saying it makes sense to use another 8 weeks of 10-milligram BID.

DR. RAUFMAN: I think the FDA should clarify that.

DR. ALTEPETER: Yes. To clarify, the sponsor's proposal is for patients who fall into this category of prior failure to TNF, that they would get 10 milligrams continuously. They would never decrease. So that's the regimen that's being asked about in this particular question.

DR. PARDI: Sorry. Let me clarify my comment then. So the same comment applies, that this isn't the overall approval of the drug for ulcerative colitis. It's if you failed an anti-TNF blocker, we're saying it makes sense to be on prolonged 10 milligrams BID because of the added efficacy.

DR. SU: May I ask for clarification? What we're seeking is for 10 milligrams to be an option as a maintenance therapy for patients who have failed TNF blockers. We're not asking approval for

every TNF failure patients to be on 10; 10 or 5, but 10 as an option.

DR. LEBWOHL: Dr. Lightdale's concern, though, is that this would be interpreted as not just an option but as a requirement to allow for giving 10 milligrams, that one would need to have taken infliximab.

DR. LIGHTDALE: I could totally foresee a scenario where you do induction with your 10 mgs BID. You now go to 5 mgs BID, and all of a sudden the patient is not looking as good, and you want to go back up to 10, and you call up -- I won't say their name again, and they say, no, they can't because you have to have had infliximab first. And again, right now that may not be a problem but maybe in five years -- anyway, you guys will work that out. I'm not going to -- it is interesting to me. It would be nicer if this was, again, that clinical judgment discussion, that there are clinical moments when it's appropriate to escalate therapy.

DR. CHANG: Could I ask a question? I guess

now I'm starting to get confused about this question. I think that the sponsor's asking that if patients who are intolerant, lost response, an inadequate response to TNF, that they have the option of 10 even though I guess potentially use 5 as maintenance. I think that's [indiscernible]. But if a patient can't get a TNF alpha inhibitor -- I think that's what you're saying -- that doesn't mean that they can't get this agent. It's just that they don't have the option to use it at 10 milligrams? Is that correct?

DR. LIGHTDALE: I mean, I could see that as being a by-the-book reading of this indication to use 10 milligrams twice a day as a maintenance therapy. I didn't mean to interject something, but it is -- what I would prefer is that concept that this is about clinical judgment, so it's really for adult patients with moderate to severe active UC who need it, and that may include patients who have had an experience now where they clearly have very active disease, so they've even failed infliximab.

That would be nicer if it was written like that and it was broader. What about the patients who've tried Humira? Do we have to go first to infliximab before we go -- anyway, but there's sanity, so we'll be okay.

DR. RAUFMAN: Additional comments or discussion?

(No response.)

DR. RAUFMAN: I'm not going to repeat all of the discussion we just had about the wording, but it's somewhat based on the studies that were done and how these trials were set up, and the data we have in front of us, which is what we're using as our evidence-based decision.

DR. GRIEBEL: This is Donna Griebel, FDA. Again, the FDA believes that both doses have been shown to be effective, so the question before you is the uncertainties and risks. If you're comfortable with the risks at both doses, then maybe it doesn't have to be a narrow population, or if there's a certain population for which you could think of the uncertainty as intolerable and there's

such a low-risk group that you could identify, then maybe those are who you say that's who the 5 milligrams is for.

I think we're stuck with the data that's given, and this is the subgroup analysis that was presented as maybe this is a group that benefits more that you could do a risk-benefit that argued for. But again, if you come back and you're not concerned about the risk with 10 versus 5, you could say that.

DR. RAUFMAN: Well, that's what I'm hearing, is I'm hearing that there's a general consensus that the benefit outweighs the risk.

Dr. Assis, did you have a comment or question?

DR. ASSIS: A brief comment, which is how [inaudible - audio gap] moving in this approval process, would something like prior use of integrins be dealt with just from a labeling perspective? Obviously, that was -- be addressed by the FDA.

DR. RAUFMAN: Does FDA want to comment?

DR. ALTEPETER: It would not be addressed because there is no data that we could use to address it.

DR. RAUFMAN: Did you heard that?

DR. ASSIS: Yes.

DR. RAUFMAN: Okay. Dr. Levine?

DR. LEVINE: Hi. Doug Levine, industry representative. Just a question on procedure. Does it make sense to ask the committee verbatim what this question is, but then add an additional question about maintenance dosing regimen in general at 10 milligrams BID? I'm just asking the question for procedural ease.

DR. GRIEBEL: It's tough to add questions. What I would suggest that folks do having listened to the conversation, if you say I'm okay with this, in your discussion when you explain your vote, you can add, but I would be happy with 10 milligrams available for every single patient because I'm not concerned about the risk, or whatever caveat you would like to add.

DR. RAUFMAN: Great. Can we move on to the

voting question?

DR. STRATE: I brought this up earlier, but I guess the data from Truven is obviously -- it's a database. It's not perfect, but I'm just wondering as a clinician are there any relative data to dual therapy, or azathioprine, or something to put this increased risk of zoster into perspective? Are there data from the literature on the risk of zoster in azathioprine or in -- because the data given was just for any anti-TNF but didn't break it down further, because I think we're treating patients with drugs that put them at an increased risk maybe equal to this. I'm not sure. I would like to have more data on that.

DR. SU: I think you were asking about the clinical data or clinician's perspective. I think it's best to ask Dr. Sandborn to give that comment. As you heard, we have very limited or no data from Truven.

DR. SANDBORN: First of all, this drug is being proposed as monotherapy, so no concomitant azathioprine or mercaptopurine, a rapid removal of

steroids once the patients achieved response. Bruce and I were trying to think earlier if we could put our hands on -- the study of zoster in TNF blocker patients has been pretty well studied, and it's not particularly elevated.

I think there are a good bit of data with thiopurines, but I can't think of a well done case control study that just nails it. You know from your practice that you see it not infrequently in some various mixture of azathioprine and steroids. There's lots of case reports in the literature of herpes encephalitis and really disseminated zoster with azathioprine. We have a number of hepatologists in the group, and I suspect they have a perspective on this as well. So I think it's accurate that it occurs with azathioprine, but I just don't have a perfect case control study.

DR. RAUFMAN: Dr. Khurana?

DR. KHURANA: I just have one quick question. What was the washout period between the previous drugs used and when these trials were conducted? That could allude to why some patients

had zoster worse than others.

DR. SU: So for azathioprine and 6-MP is 2 weeks.

DR. KHURANA: And for TNF blockers?

DR. SU: Eight weeks.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I think most of the patients that we call TNF failures, they were people that had a lost response or inadequate response. It wasn't intolerance. Is that correct?

DR. SU: That is correct.

DR. CHANG: I don't know why intolerance is in there. To me, I would feel more comfortable if it was inadequate response, lost response, because if someone couldn't tolerate it, how do you know you have to have the option of 10 milligrams? It could be 5. But maybe that's just a minor detail.

DR. RAUFMAN: I think we have an argument here between strict constructionist and loose constructionist.

(Laughter.)

DR. RAUFMAN: So the voting question,

question 4, do you recommend inclusion of this dosing regimen for this population in the product label? Any questions about the question?

(No response.)

DR. RAUFMAN: Your buttons are flashing.

(Voting.)

DR. FAJICULAY: For the record, the results are 15 yes, zero no, and zero abstain.

DR. RAUFMAN: So maybe we'll go around the table the other way. We'll start with Dr. Assis. If you could state your name, your vote, and if you want to, the reason why you voted as you did.

DR. ASSIS: David Assis. I voted yes. I felt that the -- did not provide -- [inaudible - audio gap] -- data set to make me concerned. From that standpoint, I would deprive the patients who have not responded or failed to lose -- I would hope.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: Jenifer Lightdale. I voted yes. To me, the benefits of having the 10 milligrams twice a day option outweighs the

risk, and it's nice to have that option. And I would like to put on the record that I do believe the indication for 10 milligrams BID is again probably more of a clinical judgment decision around the severity of the disease rather than just that you failed another therapy. Failing another therapy is just indication that it's a severe disease.

DR. KHURANA: Sandeep Khurana. I voted yes, but I just do want to make a point that I would leave it to the clinical judgment of the clinician to decide on the long-term maintenance dose irrespective of whatever the label said and obviously not to exceed more than the recommended doses.

DR. CHANG: Lin Chang. I voted yes. I think that the data with the TNF failures with the 10 milligrams versus the 5 milligrams and placebo was impressive enough to support that, and especially if you considered a sustained, steroid-free remission.

DR. LEBWOHL: Ben Lebwohl. I voted yes.

Despite some concerns about long-term safety of that dosage, 10 milligrams should be an option for those who failed anti-TNF therapy. But this vote should not be seen as saying that it should be exclusively reserved to those who failed anti-TNF therapy. It should be an option for others as well.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes for the reasons just stated.

DR. PARDI: Darrell Pardi. I voted yes. This is a desperate patient population. These are impressive results, and I think the safety concerns, although they are dose dependent, the difference between the 5 and the 10 were not large, and several of these are mitigable by a good dermatologic exam or hopefully a vaccine.

DR. STRATE: I'm Lisa Strate. I voted yes for the reasons that have already been stated.

MS. McVEY HUGICK: Joy McVey Hugick. I voted yes for the reasons that have already been stated.

MR. MATSON: Tracy Matson. I voted yes for

the reasons previously stated.

DR. LANE: Cliff Lane. I voted yes for the reasons previously stated and would strongly endorse the notion of providing some flexibility to the treating physicians about whether they use 5 or 10 in the maintenance phase.

DR. JONAS: Beth Jonas. I voted yes.

DR. FUSS: Ivan Fuss. I voted yes for the reasons already stated.

DR. GRAYSON: Mitchell Grayson. I voted yes for the reasons that have already been stated. However, I would say that I did not see data that would suggest to me in those that were not TNF failures that there's a reason to use the 10-milligram dose for maintenance, and I would encourage only the 5-milligram dose. I do agree that there should be the ability with the doctors, but I did not see any data there that suggested to me that there was a superiority in the 10-milligram dose in the other patients.

DR. PROSCHAN: I'm Mike Proschan. I voted yes as well. Again, there's certainly some

evidence of more benefit in the TNF failures, but I would caution that the strength of that evidence is not strong at all. I think this could easily be over-interpreting the data.

DR. RAUFMAN: Thank you. So question 5 -- and we're going to have some discussion before we vote -- do you recommend that the applicant conduct a postmarketing efficacy trial in this population comparing a 10-milligram BID continuous dosing regimen versus a regimen of 10 milligrams induction and 5 milligrams BID as maintenance?

Any discussion of the question? Any issues about the wording of the question?

DR. LEBWOHL: The question about the wording, does efficacy also imply a safety study?

DR. ALTEPETER: The safety data would always be requested in the context of an efficacy trial, but I think the intent of the question was, was a trial specifically designed and powered to demonstrate whether the higher dose is truly more efficacious than the lower.

DR. RAUFMAN: What is the strength of such a recommendation? Does this mean that the FDA will insist that the applicant conduct this trial? What does our recommendation mean?

DR. GRIEBEL: Your recommendation is pointed to when we talk about postmarketing commitments. You cannot require an efficacy trial. In limited circumstances you can when it's related to safety, but this would be a postmarketing commitment, so it would be something that would be negotiated with the applicant. But we would be looking for your comments in terms of -- I think we heard earlier comments about questions about after one year what happens if you reduce the dose, and we're open to bring those to the table, too, in this discussion.

DR. RAUFMAN: I would also be interested in a study of the efficacy of the new shingles vaccine in this population. I think that would generate some important data.

Dr. Lebwohl?

DR. LEBWOHL: I also think we should send the message that we're particularly interested in

knowing about the efficacy in underrepresented minorities.

DR. RAUFMAN: That's a good point. Additional comments, questions?

(No response.)

DR. RAUFMAN: It's not much for me to summarize there. Everybody heard that discussion.

DR. SU: Is it possible for sponsor to make a comment?

DR. RAUFMAN: It is possible.

(Laughter.)

DR. SU: We also have discussed this in terms of both utility as well as the visibility of doing an efficacy trial postmarketing comparing 10 and 5 for maintenance. I will actually ask Dr. Sands to give his perspective followed by Dr. Sandborn.

DR. SANDS: Bruce Sands. In my opinion, it would be extremely difficult to actually enroll in this study after you've approved this dosing. I think patients and physicians alike would look at this approval and look at, frankly, the data that's

already there in this randomized controlled trial and not sign up for this at all. I guess in stating my personal opinion, I'm not in equipoise for this question anymore, and for me personally, it wouldn't be ethical to actually enroll a patient in this study. So I'm quite concerned about that.

DR. SANDBORN: I agree with Bruce. I think this would be quite difficult to enroll. I take the point about Henry [sic] Peto, and it's okay to do subgroup analyses as long as you don't believe it, but that's not really what happened here. Both doses are effective, and if we didn't have some concerns about safety in the 10-milligram dose, there wouldn't have been a request for limitation. So this was sort of a voluntary narrowing of the patient population by the sponsor to try to get the benefit and safety right for maintenance.

But the effect size for 5 during maintenance and failure in naive patients is pretty big, and it's a decent size trial, and the effect size is pretty small in the failure patients. So to me it's not really the interesting question. Really,

the interesting question is what Dr. Chang has hit on several times and the sponsor's actually doing it. They're taking patients who are on 10 milligrams in the long-term extension trial, and they have hundreds of patients there, and they're offering them chance to randomize continuing 10 versus 5.

That trial's ongoing, and that's the really interesting trial to me, and to try and do this immediate post-induction, it's not the right time. The time that we're interested in is when you consolidate induction, go on for 6 months or a year, and then look to see if you can step down in patients who have deep remission.

DR. RAUFMAN: Dr. Lane?

DR. LANE: As I read the question, I think is the study that was just discussed consistent with this type of study, because it doesn't specify when the maintenance randomization dosing would occur, or was the notion that this would be right at the end of induction?

DR. GRIEBEL: I think the notion that drove

writing this question had to do with how do we deal with the uncertainty related to the subgroup analysis. That's what drove it, but what I have said was we're open to additional -- I heard a number of additional questions. The group that would benefit, is it just TNF failures or is there something else that defines that group that we should open this up to and not get locked into these paradigms? Then as Dr. Sandborn described and a number of people mentioned on the panel -- I think Dr. Chang -- when can you step down on the dosing? So we're open to hearing other discussion of potential postmarketing commitments.

DR. CHANG: Comment?

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I'm just wondering if there's a way the sponsor could look through all the data they have to determine if there are patients, for example, that were in clinical remission in the maintenance and if those patients, maybe in the open label, again, like I said -- to go with the 5. I'm just trying to feel do you have data other than

just doing it now and offering 5 milligrams.

Is there any data that you could look at that would help guide you in the clinical management of patients that would be ready to go to 5 milligrams? I wouldn't say clinical response, but maybe clinical remission. I'm just trying to figure out -- I get the feeling that you feel that everyone should stay on 10 milligrams maintenance and not go to 5. Is that correct?

DR. SU: Well, our proposal is that 10-milligram maintenance be a consideration for TNF treatment failure patients, and ultimately the decision of who gets 10 versus 5 amongst the TNF treatment failure patients and how long to stay on 10 is going to be a clinical decision.

We have looked extensively at our data, looking for which populations may benefit more or 10 versus 5, and ultimately TNF treatment failure is the only subgroup that really came out that's clinically meaningful and that consistently shows that difference. We have also further censored who amongst the TNF treatment failure patients -- I can

ask Dr. Maller to provide further data if that may be useful.

DR. CHANGE: No. I'm just trying to get back at what Dr. Sands and Dr. Sandborn said. They don't think it's correct or it would be hard to recruit for a maintenance study where you do 10 milligrams continuous or 5 milligrams. I think that's what they were saying. So my feeling must be that when it's available, they would just use 10 milligrams maintenance. That's what I'm assuming that they're saying. But I'm also wondering if maybe a study like this would be for people who are not TNF failures.

DR. SU: So as far as what clinicians will do once they decide to place TNF treatment failure patients on 10 and how long and what they would do, I'll let Dr. Sandborn comment on that. The study that Dr. Sandborn and others might have mentioned is a study that we're looking at, is taking patients who are doing well on 10 milligrams and comparing staying on 10 versus going down to 5. That is not limited to TNF treatment failure

patients.

DR. SANDBORN: The experiment you're talking about just a second has basically already been done. The non-failure patients, the difference between 5 and 10 at a year was 4 percent, and both patients did really well with an NNT of 3. And I think Dr. Maller said that they did 1300 combinations of baseline demographics trying to predict, and the only thing that fell out of all of that was the TNF blocker predictor. So they've really done their best shot at finding a predictor, and that's what it was. And then if you apply that predictor across all kinds of outcome measures, the results are consistent, so I think it's real.

I wouldn't want to be characterized as saying that I intend to treat with 10 forever in these anti-TNF failure patients. I don't think that will be the case. Our practice is routinely to look for endoscopic remission 4 to 6 months out, and if the patients are doing great and they've got endoscopic remission, I suspect that many times the patients will want to step down at some point later

in the course. And the cool thing here is you're not going to immunize them if you do that, which is different from a biologic where you step down and you sometimes risk immunizing them and stuff.

Again, the study that they're running where they're pulling patients out, remember there were responding patients who got out at the end of the trial and ended up on 10, and some of those could be stepping down, too. So I'd bet the step-down trial is heavily anti-TNF failure patients, but it's not going to be all anti-TNF failure patients for the trial they're running now, the late step-down trial.

DR. CHANG: Just to clarify -- so I'll just make, and then we can close it is that in non-TNF failure patients, to you it's clear that 5 and 10 is pretty comparable. In the TNF failures, it's more clear that 10 milligrams would be beneficial. So you wouldn't really want to enter them in a trial for maintenance of randomizing to 5 and 10. Is that correct?

DR. SANDBORN: Right. I think that's how

Bruce and I see it, although I totally agree with Dr. Pardi that a number of these -- the dose-dependent things, really in the UC program itself as compared to rheumatoid arthritis, we didn't see a very strong signal for serious infection being dose related. But if you take the totality of all the indications with 10 milligrams, that looks more real, so I think it's probably true.

But what we saw in the UC program is non-melanoma skin cancer and herpes zoster. So if I think there's a good shot in the naive patients, taking account of what Dr. Lightdale said, it would be nice to have a little bit of flexibility for the patient that they feel like they're going to be really sick and you'd like to give them 10. But other than that, for the typical moderate to severe anti-TNF naive patient, I think I'm going to try and step them down for safety because the benefit just didn't seem there, whereas for the failure patients, I'm probably going to go for a while, but it's not going to be forever. I probably will step

down a lot of those patients, eventually.

DR. RAUFMAN: Thank you.

Dr. Proschan, did you have a comment?

DR. PROSCHAN: I agree with the sponsor with the comment that if there was no concern for safety, then you'd have a real hard time getting anyone to sign up and you could say it would be unethical. But I do think that the safety question's big, and I think when you take that into consideration, I think you could get patients probably to sign up for it. It depends on what you say to them. If you say this is already an answered question, of course no one's going to sign up, but if you say we have some safety concerns and we want to make sure everything's good, then I think there would be a different response.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I want to echo the concept of also rolling in the zoster vaccination question, and actually I think a very nice trial could be a zoster vaccination trial comparing 10 milligrams to 5 milligrams as maintenance. I'll put that out

there. That's a wish list.

DR. RAUFMAN: Just to summarize, because I think we can move ahead to a vote here, is that I think several of us around the table are not quite clear that this is the postmarketing trial that we'd like to do; that there are a number of different ideas for an interesting postmarketing trial. So we can vote on this, and people can make their comments when they explain their votes. So the buttons are flashing, so you're voting yes if you recommend; no, if you don't recommend this.

(Voting.)

DR. FAJICULAY: For the record, the results are 7 yes, 8 no, and zero abstain.

DR. RAUFMAN: Let's start with Dr. Proschan. We'll go around that way.

DR. PROSCHAN: Mike Proschan. Just what I said a minute ago, I think safety is a big issue, and I think it would be very nice to have real evidence on the safety comparison to be able to make a decision, and I don't think we have great evidence on that right now.

DR. GRAYSON: Mitchell Grayson. I voted yes. Actually, it was Dr. Proschan's comments before about the data, that we really can't make -- that the issue that the p-value is not that big and that the difference between the two isn't that clear says to me that we need to do a better study, and this would be the better study. And there is a safety issue. I don't believe that the 5 and the 10 are equal. There is a safety signal coming out in the 10. So I think they have to do this, honestly, and that's the reason I voted yes.

DR. FUSS: Ivan Fuss. I also voted yes for very similar reasons as my colleagues just mentioned. In addition to the study, if life is good, I would like to see this study data and compare it with stepping down the data, a study that Bill Sandborn has mentioned. I think between both studies, you would get safety data as well as efficacy data that would prove fruitful.

DR. JONAS: Beth Jonas. I voted yes. I appreciate that this study may be hard to do, and I know that when your boots are on the ground trying

to do clinical trials, it's hard. But I still think there's enough uncertainty around this question in these TNF failures that we need more data. We don't have a lot of numbers around the efficacy if you really look at that very carefully, and the differences are small. And I do think that there's a safety signal that's worth exploring further.

DR. LANE: Cliff Lane. I voted yes from the perspective that I think it's very important that there be a postmarketing study. I think the longer that study, the better, because I think the long-term consequences of the disease and the long-term consequences of immunosuppression are very important to sort out with this particular agent. My vote shouldn't necessarily be taken that to be randomization after 8 weeks, but that there be some study that addresses those issues.

MR. MATSON: Tracy Matson. I voted no.

MS. McVEY HUGICK: Joy McVey Hugick. I voted no because I do feel like the existing studies that are ongoing by the sponsor will give

us some of that safety data that we're not sure about right now. So I felt that because recruitment might be challenging and you may have a hard time getting patients to enroll in the study, that I didn't want to impose that.

DR. STRATE: I'm Lisa Strate. I voted no. To this specific study, I think it would be helpful to include the vaccine and some other studies as mentioned.

DR. PARDI: Darrell Pardi. I voted no because we just approved this language based on the preponderance of evidence, so I'm not sure what doing another study would do to that decision. And I think the more interesting question is being addressed, which is when patients are doing well, can we step down safely?

DR. RAUFMAN: Jean-Pierre Raufman. I voted no for that reason and reasons articulated by others, that I think there are more interesting and pressing studies that need to be done regarding this issue. And I was convinced by Dr. Sands and Sandborn that it would be difficult to actually do

a comparison study at this point.

DR. LEBWOHL: Ben Lebwohl. I voted yes. While I found that the stratified findings regarding anti-TNF failures were compelling, I agree with Dr. Proschan's comment that these findings aren't strong enough that that should set us in stone for many years to come with regard to who gets 5 and who gets 10.

DR. CHANG: I voted no for the reasons that were stated previously.

DR. KHURANA: Sandeep Khurana. I voted no.

DR. LIGHTDALE: Jenifer Lightdale. I voted no for all the reasons that were said. Just restating quickly, this is not to say that there shouldn't be postmarketing studies. There absolutely must be, but there are better questions to ask than that one.

DR. RAUFMAN: Dr. Assis?

DR. ASSIS: Dr. Assis. I voted yes. I believe that this would be the first time that the higher dose would be used, so I think the burden might be a bit higher to show the safety. Clinical

judgment goes a long way, and without any guidance, I think many [inaudible - audio gap] -- to reduce the dose. So I think, particularly for young patients, who -- a long-term risk of cancer and be hesitant.

DR. RAUFMAN: Thank you. The next discussion question, please discuss if additional postmarketing evaluation of safety is warranted and the mechanisms you recommend, for example, registry, observational study, et cetera, for such evaluation. I think this question's pretty clear, so I'll open it up to discussion.

Dr. Grayson?

DR. GRAYSON: Following back on my comment about safety, I think you absolutely need some postmarketing safety study, whether it be a registry, I think that's fine, just something to collect the data events and somebody to be looking at those to see if a signal pops up. And we don't really know what will happen, especially at the higher dose with years of treatment. And this is the only way you're going to find out, so

absolutely.

DR. RAUFMAN: Dr. Lane?

DR. LANE: Cliff Lane. I think it was hard for us, voting on 5 and just discussion on 6, to parse out efficacy and safety. I think one could have a postmarketing study. If well designed, it could address some of those unanswered questions. I would strongly urge that it be done in the context of a study as opposed to something like a registry.

DR. RAUFMAN: Dr. Chang?

DR. CHANG: Actually, I agree with that. I think it should be something a little more structured with the guidance of the IBD experts. If they're following the patients, what are the things that they would want to do and follow annually, or every month or whatever, to look at maybe potential predictors or increased risk factors for getting these adverse events? So I would prefer for it to be a little more structured.

DR. RAUFMAN: I would add colleges along with an ID person. Right. There may be reasons

why we could ignore the cancer signal here, but I don't think I'd like to ignore it, and I think that postmarketing surveillance of that would be very important.

Dr. Lightdale?

DR. LIGHTDALE: I actually think postmarketing studies must be done, like very specific studies. But I think a registry would be important because what I'm seeing, of course, are patients don't do well on meds -- there will be patients who don't do well on this medications, and they will go on to other medications. And we need to keep track of the fact that they were exposed to this and make sure that we pick up that signal hopefully in 10 or 15 years; no offense. But we need to be keeping our eyes on this ball.

DR. PARDI: I think a registry, if it's rigorous enough, could answer some of these questions. Studies, you're going to get a certain number of patients that enroll and some that won't based on convenience or traveling back to the medical center, or whatever it is, whereas a

registry, it's easier to enroll the patient and just follow them in real world.

DR. RAUFMAN: Here's a difficult question. We can continue and finish this discussion in the next 45 minutes or so or take a break in a few minutes. I can go either way. Is there a general consensus? Is there a consensus there to finish?

All right. No vote, we just finish. If you disagree, say something.

Any other discussion on this discussion point? It is not a vote.

(No response.)

DR. RAUFMAN: Just as a general summary here is that there's a consensus that postmarketing surveillance is important for safety issues regarding the potential risk of infectious disease, again, interest regarding the new shingles vaccine and whether that will alter the shingles signal that we're seeing with the higher dose of this drug. There was some enthusiasm for a registry here, that detailed, well-run registry would perhaps address this issue.

We can go to the last -- this is probably going to be a long discussion. Let me read through this.

Please discuss the following:

A. Any unique characteristics of the pediatric UC population that should be taken into account when planning the tofacitinib pediatric development program. Please consider the ontogeny of the immune system and the described mechanism of action of tofacitinib.

Given the safety benefits, malignancy, and serious infections described with long-term use of 10 milligrams BID and the severity of UC in the pediatric population, please recommend the maximum dose that should be targeted for evaluation for long-term treatment in pediatric UC.

C. Please discuss whether you recommend limiting enrollment in the pediatric trials and subsequent pediatric indications to patients who have failed other biologic therapies.

To start the discussion, one thing I'm not seeing here is what the definition of the pediatric

population is. I heard two years. I heard four years. Dr. Grayson?

DR. GRAYSON: I think that's one of the key points to this because I know the applicant is proposing two, and I would say I'm a little worried about two just because I think in terms of the immune system in development, you do see a significant difference up until about the age of 4 to 6, and then I think you're in better shape coming out of that.

So I'm a little worried about that 2 to 4 or 5-ish age and how that might impact on the developing immune system. I'm a little bit relieved I guess -- I don't know if that's the right word -- about the data with vaccines and suggesting that that's not having as much of an impact at least with varicella. Now whether that applies broadly, I don't know. And that suggests that maybe what we thought of JAK inhibitors is that it's not quite as bad as it would be on the immune system developing. But I have some concern of that in that age group, so I'm not sure I would

go down to 2, and I certainly would not go below that. Then I think we'd have potentially serious impairments of the immune response.

DR. PROSCHAN: We have pediatricians around the table.

DR. ALTEPETER: May I ask a clarification to that? I completely appreciate the point, and there is more concern the younger down you go and the less developed the immune system is. But in your mind, do you make a distinction with this mechanism of action versus others? Would you have the same concern with the use of a TNF in a young patient?

I think we struggle with the issue that although all these concerns exist, there are also patients, very unlucky occasional kids who get this disease in that age group, and we want to make sure, if it's appropriate to do so, that they have access to these drugs.

DR. GRAYSON: My concern really is the broad effect on stats. So no, the TNF inhibitor I wouldn't be as worried about it. So how that impairment of the stat functioning, 1, 2, and 3

primarily -- but in terms of the development of the immune response. And you don't really have your full humoral immune response sort of kicked in and everything until somewhere in that 4 to 6 range.

That's where I'm worried about it. I'll be honest with you. It is a theoretical concern. I'll be fair. Based on mouse stuff, I would expect JAK inhibitors to have had a lot more problems in humans than they have, just proving that humans aren't like mice, for anyone who wants to get a great quote. So it is a theoretical concern. I guess it has to be balanced. But I'm just worried that when you start doing these trials, you've got to be very careful in that age group, and that's really what my concern is with that.

DR. RAUFMAN: Dr. Fuss?

DR. FUSS: I have a similar concern as Dr. Grayson brought up, is the effect of this drug on the stats. The stats are going to be one of the major pathways in developing cells. If you look at their effects, at least in mouse models, in a mouse model that is, quote, "equivalent to what you would

see in a long infant," you should have a lot more effects than what we're seeing.

That being said, when you're dealing with pediatric UC, as I may have mentioned before, there are a lot of factors that you've got to look at in deciding what type of UC do they have. In this case, exon sequencing is going to be very important to rule out a lot of monogenic type diseases or an ulcerative colitis-like picture.

The reason I bring that up is not only drugs that are going to affect the immune system, but a lot of these monogenic diseases, we already know that a lot of these biologics don't work in them and that some of them actually have to go to bone marrow transplant. So it's very important when looking at the pediatric population that a study will include or must really include an exon sequencing of a pediatric population before you start enrolling them, especially in these young children.

Just as an aside, one of the other JAK inhibitors that is already approved when it's used

off label -- and it is used off label a lot of times in patients with immunodeficiencies when they're going to bone marrow transplant to try to inhibit arms of the immune system. We really don't use it under 3 years of age. So it's a more clinical observation, but again, you're really affecting a large portion of the immune system that I wouldn't be comfortable looking at and using in that kind of age group.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I guess I would point out that there's obviously a lot of interest these days in what's called "very early onset IBD," so VEO IBD. And it just seems like that population probably ought to be put over here. That's the clinician speaking.

The clinician speaking will also point out that ulcerative colitis in a very young child is a tricky diagnosis to make, and you always do it with the caveat -- the families practically can recite it back to me. "Probably UC" is the way I diagnose them. I've made every argument on why I don't

think it's UC, or I do think it's UC and I don't think it's Crohn's. But you have to be super-super careful calling it UC for sure in a very young child, and that's just borne out historically. Nobody seems to be able to move that dial very much.

I guess to this 2 or 4 discussion, yes, I'd be a little careful getting below 4. I do think that there are desperate families, and I've been around them, and it's not fun. And they are sitting there with a child who's bleeding out often, and you're giving lots of blood products, which isn't good either, let alone steroids. We use worse medications than methotrexate and 6-MP to get this under control, and steroids don't work.

So this is something you don't want to be not offering to them if it's going to turn out -- that we understand the mechanism, we can identify who it's going to work for, and we can offer it to them. From a trial perspective, though, yes, I'd be careful to go down too low.

DR. RAUFMAN: If I could get clarification

from FDA regarding item B, the long-term use of 10 milligrams BID, the way we're to consider that, is that weight based, based on 10 milligrams for an adult that it would be an equivalent weight-based dose for a child?

DR. ALTEPETER: The idea would be a weight-based dose would be selected to target the average exposure that adults have with the 10-milligram dose, so an equivalent dose adjusted for the size and weight of the patient.

DR. RAUFMAN: Dr. Lightdale, given your previous comments, how do you feel about the dosing?

DR. LIGHTDALE: I think we rely in general on weight-based dosing in pediatrics, and then usually we have a maximum. At some point, the child's weight is literally high enough that you're now into the adult doses, and we max out and give an adult dose. I'm sure they can tell us how to work with it. I was happy to hear it was a suspension as well as a pill. That makes a big difference in pediatrics, so that's terrific.

Can I make one other comment that I have been thinking about since last night? And I would sort of push this actually over to you guys to ask your opinion.

I actually think a major issue you have to think about with pediatrics is exposure to EBV, Epstein-Barr virus. And we do routinely look at EBV serologies prior to starting almost anything just so I know where I'm starting, and I will tell you, there are few things that make me more worried than one of my patients having acute mono, and it's not fun when they're on their virus biologics, et cetera. So to me, that has to be thought about as you're going into this. You're going to need to know the EBV status of your patients.

DR. RAUFMAN: Dr. Fuss?

DR. FUSS: Actually, in response to this, Jenifer -- and actually I wanted to ask this previously for clarification from the sponsor, if they can. In the literature that was given to us, in patients who had developed malignancies, there was some exposure previously to various viral

etiologies that they thought might be contributing to the malignancy.

There is literature. Basically there's an article by Endo et al. in Onco Target from 2016 where it actually shows the reverse, that they looked at tofacitinib's effect on cell cycle, proliferation, and tumor growth in Epstein-Barr virus associated T and natural killer lymphoma cells and actually found that tofacitinib actually decreased cell cycle, proliferation, as well as decreased EBV virus proliferation and lymphoma transformation. So there's sort of a disconnect or maybe we don't have a enough data. And that's why I pose it, what does the sponsor think as far as EBV etiology and its long-term effects.

DR. SU: As far your question, it's the biology. I would ask our infectious disease specialist, Dr. Schooley, to give his comment. We clearly do not have the exact data that you were asking for from our development program.

DR. SCHOOLEY: Dr. Lightdale, I think your question's a great one, and I would strongly

endorse getting baseline data because I think it's the only way to interpret the data when you see how it rolls out in the clinical experience in children. As you and all the pediatric folks know, the two waves of seroconversion occur between zero and 2, and then when people get to dating age. So the kids that are going to be in this trial will include a much larger number of people who'd be at risk for primary infection. That would be the situation and would be one way we need to know the most.

We already know in the adult population that 95 percent of adults are EBV seropositive by the time they get to 20 or so. This patient population isn't getting transfused like a lot of the other patient populations that get transplanted and end up having primary infections after they're on immunosuppressives and some of the things that we see in the post-transplant lymphomas.

So I think in the pediatric population, the baseline data will be important. It will be important to understand how to manage acute EBV

infection should it occur as these studies proceed. I think that's a very good question. I think we'll learn about both the clinical approach and also a lot about the metabiology of EBV to get to your question about this very interesting kind of paradoxical question; so great questions.

DR. RAUFMAN: Dr. Assis, you had a comment or a question?

DR. ASSIS: Yes. I would just echo some of the other comments regarding in terms of [indiscernible] in very young children, humoral development. But I would add also for [inaudible] there that it would be nice perhaps to not have the burden of failing therapies prior to starting this drug. It's a good avenue for kids or teenagers to start with an oral drug and not have to go through the hoops that adults may need --

DR. RAUFMAN: Dr. Chang?

DR. CHANG: I'm just wondering more about the induction dose of this 10-milligram BID. It just seems high to me in 2 year old to 4 year old, and I'm just wondering is there data to support

that. Also, this pharmacokinetic data they're using from juvenile idiopathic arthritis, I thought that was treated by 5 milligrams BID. Is there really comparable evidence that you should be starting that at that level for a very young population given -- I don't know if you'd even know the benefit of that versus not knowing the risk.

DR. SU: We don't have data in the pediatric UC patients. That's our intent to study. I will ask our clinical pharmacologist to explain the dosing rationale for selection of the dose to be studied in the JIA population, which was obviously in discussion based on discussion with our regulatory agencies. Both 5 milligram and 10 milligrams, or an equivalent dose, were studied in the JIA population.

DR. MUKHERJEE: Arnab Mukherjee, clinical pharmacology. I'd like to clarify that we adjust the dose by weight for the child's body weight to target exposure equivalent to 10 BID. We will not give the full 10 BID dose to every child. And on that basis, on the body-weight adjusted basis,

younger kids with a lower body weight will get a lower dose.

Can I have slide BD-8 on the screen, please? Actually, 3, number 3, please. The table below provides the recommended doses by body weight. For body weights let's say between 10 and 18 kg, they'd get a 7-milligram BID dose, and that dose will equal the exposure, the C average of 10 BID in adults.

One of the things that we have seen is that at the younger body weights, the volume of distribution is lower in the youngest kids, and that leads to a higher Cmax. As explained by the FDA, once you are below about 30 kgs of body weight, the exposure, the Cmax is about twice that you would see in the older kids. And for that reason and for an abundance of caution, we restrict the exposure in the youngest and the less than 30 kg to only 5 BID. This is only out of an abundance of caution. In our adult program, we don't see any correlation with the Cmaxes, so it's really the C average or the AUC that's the driver

of efficacy.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I just would make sure that I've put on the record that pediatric ulcerative colitis is a serious disease. It's quite significant when it presents. It's usually a pancolitis, fulminant colitis, and the quickest way to have failure of a drug is to give an underdose.

So just to really make sure that in the process of making sure we're designing a trial well for kids, that we're not so worried about children that you're actually underdosing them because that will actually do the biggest disservice. And if this drug works as well as they're saying it works, I want it to work for kids. There's nothing like a disregulated immune system to get your attention, but I think you need to get the immune system under control, and that may take doses that surprise you, but it's a serious disease.

DR. RAUFMAN: So that's a good segue into C, so would you recommend limiting enrollment in these trials to children who have failed other biologic

therapy?

DR. LIGHTDALE: I think you're looking at me. All right. Jenifer Lightdale again. It's a great question. You could play it either way. I mean, I think right now those are the most desperate, and if I think like most clinicians, most of us will reach for the medications we're most comfortable with. It actually took a while to get comfortable with infliximab for ulcerative colitis just as it was taking a while for I think adult gastroenterologists also to understand it in moderate to severe ulcerative colitis. You have to give much bigger doses than you expected, and we'll try to usually induce remission first with something else and then start the infliximab so it's not leaking out of them as fast as you're putting it in. So all of that is medication we're much more comfortable with. I think getting more comfortable with adalimumab, too, as well as Entyvio these days.

So sure, I guess you could fail a couple of those before you go to this, so it's more you're

really -- but at that point it's truly your sickest kids, and this is where I look at Ivan and I'll look at Mitch, too. These are kids whose immune systems are not normal, so then it's how do you interpret the results of what you're getting because their immune systems are very difficult to control as opposed to the kids that responded to the infliximab.

DR. RAUFMAN: Dr. Grayson?

DR. GRAYSON: Mitch Grayson. I'm going to disagree with you, Jenifer, on that. I actually think that there's a chance that this would work really well, and I don't really -- with the caveat that I'm an allergist and I don't treat these kids, but to me I think I would not put that restriction on there.

I have a feeling that this might actually, in the right age group, be really good and very efficacious, and I wouldn't force them to go through everything to get to that point, especially for the trials, because then you'll have some idea and definitely you're watching the safety points.

So for this, I don't feel like having a failure is a good way to identify them.

DR. SANDBORN: Dr. Raufman, could I ask a question as a clinician? I'm an adult GI, but I do see teenagers, and it would be great to hear Jenifer's perspective on this, especially in this 10-ish range or something, you're really worried about growth, so systemic steroids are not ideal. And there's an unequivocal signal of the hepatosplenic T-cell lymphoma in young males as well as non-Hodgkin's lymphoma, the primary EBV infections that we're talking about.

So thiopurines, in addition to lack of efficacy, have really important safety signals in kids. And then if you go down this path, you have potentially the unintended consequence of forcing kids on to oral thiopurines, and did you really want to force all of them through biologics before they get this?

I wonder whether this ought to be, in part of the population, looked at as a first-line kind of advanced therapy even not necessarily pushing

everybody through steroids and immunosuppressives.

DR. RAUFMAN: We're going to have to limit the applicant's role to clarification and not additional statements. Additional discussion of these points?

DR. ALTEPETER: I would appreciate hearing from, in particular, the peds GI folks on the panel as to if you would envision yourself being open to enrolling your newly diagnosed patients in a trial like this, if that were an option that the agency and sponsor concluded was appropriate from the safety risk-benefit standpoint.

DR. FUSS: Yes, I would be open. The only concern I have is some of the side effects of the biologic, as well as this drug, can be GI perforation. In these bad UC patients, that is one of the big complications we can see. That being said, that's why we would be doing the study. But yes, I would be open to using this as a first line.

DR. LIGHTDALE: I would echo that. And to Dr. Sandborn's question, I'd actually also say sure. I think all of us are getting the heebie-

jeebies now around those thiopurines; they're not fun. So we're more and more going straight to biologics, and this is an oral biologic, which is fantastic and has perhaps a different mechanism of action. Perhaps it's safer. So, sure.

DR. RAUFMAN: Any additional comments, discussion? Dr. Lane?

DR. LANE: Cliff Lane. Just a couple of comments. There's often the notion that we do the pediatric studies to confirm that children will respond like adults. I do think there's a chance here to move the field as opposed to just confirming. So again, the idea of primary therapy to me seems very attractive as an option; not being a pediatrician or a gastroenterologist, but I think it's quite a good idea.

With regard to the study design that was proposed, it struck me as unusual that the adults didn't feel there was equipoise at randomizing to 5 or 10, but the pediatric study randomizes to placebo 5 or 10. So I just wonder whether or not secondary randomization to placebo is appropriate.

Again, I would defer to others, but just consider that.

Then the third point is some of these children will likely be getting their childhood immunizations during the time they're on study, and having some measurement of their immune responses might be helpful.

DR. ALTEPETER: Just to clarify the reason for these study designs, as they've been done in the past -- and this is sort of modeled after that -- is that the adult program had the placebo arm in induction, and that's not what they're proposing for the kids. So the idea would be that everyone would get open-label induction therapy, and then the placebo arm, and getting some control group for kids who were treated with placebo tends to happen in maintenance.

That's a historical design that's been used because in the past, the pediatric GI community had indicated that it would not be acceptable, or feasible, or operationally possible to do an induction placebo-controlled trial in kids. But

it's an issue that we struggle with all the time in terms of how to actually get interpretable data in pediatric UC patients, and we're certainly open to hearing what people think would be a potential alternative.

DR. RAUFMAN: Any additional questions, comments? Dr. Lebwohl?

DR. LEBWOHL: Ben Lebwohl. In light of the discussion we had earlier about whether the stratified findings regarding TNF failure was real or artifactual, I wonder if the proposed trial going forward could not only include both TNF nonresponders and TNF naive patients, but also be adequately powered so as to detect for formal interaction between dose and TNF responsiveness.

DR. RAUFMAN: Dr. Proschan?

DR. PROSCHAN: I think that would be nice in an ideal world, but realistically the sample size you need to detect an interaction is quite large, so I'm not sure that's really feasible here.

DR. RAUFMAN: Is FDA satisfied with the discussion?

DR. GRIEBEL: Yes. Thank you.

Adjournment

DR. RAUFMAN: We'll move on to adjournment.

We will now adjourn the meeting. Panel members, please leave your name badges -- oh, these, I wasn't going to take this home -- here on the table so they may be recycled. Please also take all personal belongings with you as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 3:37 p.m., the meeting was adjourned.)